



Effective Health Care Program

Comparative Effectiveness Review
Number 33

Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults



Agency for Healthcare Research and Quality
Advancing Excellence in Health Care • www.ahrq.gov

Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults

Prepared for:

Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
540 Gaither Road
Rockville, MD 20850
www.ahrq.gov

Contract No. 290-02-0016I

Prepared by:

RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center,
Research Triangle Park, North Carolina

Investigators:

Bradley N. Gaynes, M.D., M.P.H.
Linda J. Lux, M.P.A.
Stacey W. Lloyd, M.P.H.
Richard A. Hansen, Ph.D.
Gerald Gartlehner, M.D., M.P.H.
Patricia Keener, M.A.
Shannon Brode, M.P.H.
Tammeka Swinson Evans, M.O.P.
Dan Jonas, MD, M.P.H.
Karen Crotty, Ph.D.
Meera Viswanathan, Ph.D.
Kathleen N. Lohr, Ph.D

This report is based on research conducted by the RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. 290-02-0016I, TO #2). The findings and conclusions in this document are those of the author(s), who are responsible for its content, and do not necessarily represent the views of AHRQ. No statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help clinicians, employers, policymakers, and others make informed decisions about the provision of health care services. This report is intended as a reference and not as a substitute for clinical judgment.

This report may be used, in whole or in part, as the basis for the development of clinical practice guidelines and other quality enhancement tools, or as a basis for reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products or actions may not be stated or implied.

This document is in the public domain and may be used and reprinted without permission except those copyrighted materials that are clearly noted in the document. Further reproduction of those copyrighted materials is prohibited without the specific permission of copyright holders.

None of the investigators has any affiliations or financial involvement that conflicts with the material presented in this report.
--

Suggested citation: Gaynes BN, Lux L, Lloyd S, Hansen RA, Gartlehner G, Thieda P, Brode S, Swinson Evans T, Jonas D, Crotty K, Viswanathan M, Lohr KN. Nonpharmacologic Interventions for Treatment-Resistant Depression in Adults. Comparative Effectiveness Review No. 33. (Prepared by RTI International-University of North Carolina (RTI-UNC) Evidence-based Practice Center under Contract No. 290-02-0016I.) AHRQ Publication No. 11-EHC056-EF. Rockville, MD: Agency for Healthcare Research and Quality. September 2011. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see

<http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm>

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (<http://www.effectivehealthcare.ahrq.gov>) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly.

We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

Carolyn M. Clancy, M.D.
Director
Agency for Healthcare Research and Quality

Jean Slutsky, P.A., M.S.P.H.
Director, Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Stephanie Chang M.D., M.P.H.
Director, EPC Program
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Sonia Tyutyulkova, M.D., Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Acknowledgments

The investigators deeply appreciate the considerable support, commitment, and contributions of the EPC team staff at RTI International and the University of North Carolina. We express our gratitude to RTI staff Amy Greenblatt, B.A., Andrea Yuen, B.S., and Laura C. Morgan, M.A., Research Analysts, Megan Van Noord, M.S.L.S., our EPC Librarian; and Loraine Monroe, our EPC publications specialist.

Technical Expert Panel

We extend our appreciation to our Technical Expert Panel: William L. Bruning, J.D., M.B.A.; Allen Daniels, Ed.D.; Ronald M. Glick, M.D.; Mustafa M. Husain, M.D.; Sarah H. Lisanby, M.D.; Glenda M. MacQueen, Ph.D., M.D.; David L. Shern, Ph.D.; Michael Edward Thase, M.D.; and John W. Williams, Jr., M.D. All provided thoughtful advice and input during our research process.

William L. Bruning, J.D., M.B.A.
President and CEO
Mid-America Coalition on Health Care
Kansas City, Missouri

Allen Daniels, Ed.D.
Vice President of Scientific Affairs
Depression and Bipolar Support Alliance
Chicago, Illinois

Ronald M. Glick, M.D.
Medical Director of Center for Integrative
Medicine, University of Pittsburgh
Medical Center
Department of Psychiatry
University of Pittsburgh Medical Center
Pittsburgh, Pennsylvania

Mustafa M. Husain, M.D.
Professor of Psychiatry and Internal
Medicine Director
Neurostimulation Research Lab Chief
UT Southwestern Medical Center at Dallas,
Texas

Sarah H. Lisanby, M.D.
Director, Division of Brain Stimulation &
Therapeutic Modulation
Columbia University College of Physicians
and Surgeons
New York State Psychiatric Institute
New York, New York

Glenda M. MacQueen, Ph.D., M.D.
Head, Dept. Mood Disorders Research
Program
Psychiatry and Behavioral Neurosciences
McMasters University
Hamilton, Ontario

David L. Shern, Ph.D.
President and CEO
Mental Health America
Alexandria, Virginia

Michael Edward Thase, M.D.
Professor of Psychiatry
Mood and Anxiety Disorders Treatment and
Research Program
University of Pennsylvania

John W. Williams, Jr., M.D.
Former Director, Duke Evidence-based
Practice Center
Duke University and Durham VA Medical
Center
Durham, North Carolina

Peer Reviewers

We gratefully acknowledge the following individuals who reviewed the initial draft of this report and provided us with constructive feedback. The peer reviewers were asked to provide comments on the content, structure, and format of the evidence report. Their comments and suggestions formed the basis of our revisions to the evidence report. Acknowledgments are made with the explicit statement that this does not constitute endorsement of the report.

Stuart Eisendrath, M.D.
Professor of Clinical Psychiatry
Director of Clinical Services
Director, Depression Center at Langley
Porter
University of California at San Francisco
San Francisco, California

Edward Friedman, Ph.D.
Associate Director of the Mood Disorders
Treatment and Research Program
Western Psychiatric Institute and Clinic
University of Pittsburgh Medical Center
Associate Professor of Psychiatry
University of Pittsburgh

Ronald Glick, M.D.
Department of Psychiatry
University of Pittsburgh School of Medicine
Pittsburgh, PA

Steven D. Hollon, Ph.D.
Professor of Psychology
Psychological Services
Vanderbilt University

Sarah H. Lisanby, M.D.
Director, Division of Brain Stimulation &
Therapeutic Modulation
Columbia University College of Physicians
and Surgeons
New York State Psychiatric Institute
New York, New York

Evette Ludman, Ph.D.
Senior Research Associate
Group Health Institute
Group Health Cooperative
Seattle, Washington

Glenda M. MacQueen, Ph.D., M.D.
Head, Dept. Mood Disorders Research
Program
Psychiatry and Behavioral Neurosciences
McMasters University, Hamilton, Ontario

Andrew Alan Nierenberg, M.D.
Professor of Psychiatry, Harvard
Massachusetts General Hospital

Eric Plakun, M.D.
Psychiatrist
Austin Riggs Center
Stockbridge, Massachusetts

Greg Simon, M.D., M.P.H.
Senior Investigator
Group Health Cooperative
Center for Health Studies
Seattle, Washington

Contents

Executive Summary	ES-1
Introduction	1
Burden and Costs of Disease	1
Purpose of This Report	3
Included Interventions	3
Electroconvulsive Therapy (ECT)	3
Repetitive Transcranial Magnetic Stimulation (rTMS)	5
Vagus Nerve Stimulation (VNS)	5
Cognitive Behavioral Therapy (CBT) or Interpersonal Psychotherapy (IPT)	6
Pharmacologic Interventions	6
Patient Populations Included	6
Scope and Key Questions (KQs)	8
Organization of the Report	8
Methods	10
Topic Development	10
Technical Expert Panel	10
Literature Search	11
Databases and Search Terms	11
Analytic Framework	11
Study Selection	12
Data Extraction and Analytic Strategy	15
Treatment Resistant Depression Definition and Tier Classification	16
Psychiatric Diagnosis	17
Nonpharmacologic Intervention Treatment Characteristics	17
Antidepressant Medication Treatment Strategy	18
Disease Severity	19
Quality Assessment	19
Applicability Assessment	20
Grading Strength of a Body of Evidence	20
Data Synthesis	21
Peer Review	22
Results	23
Introduction	23
Key Question 1: Organization of Results	26
Key Question 1a: Nonpharmacologic Interventions—Overview of Head-to-Head Comparisons	27
Strength of Evidence: Tier 1 (TRD)	28
Key Question 1a: Nonpharmacologic Interventions—Key Points of Head-to-Head Comparisons	29
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation	29
Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation	29
Key Question 1a: Nonpharmacologic Interventions—Detailed Analysis of Head-to-Head Comparisons	29

Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation	29
Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Magnetic Stimulation.....	33
Key Question 1a: Nonpharmacologic Interventions—Overview of Active Versus Control Comparisons	35
Strength of Evidence: Tier 1 (TRD)	36
Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Key Points of Active Versus Control Comparisons.....	37
Electroconvulsive Therapy Versus Sham	37
Repetitive Magnetic Stimulation Versus Sham	38
Psychotherapy Versus Control.....	39
Vagus Nerve Stimulation Versus Sham.....	39
Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Active Versus Control Comparisons.....	39
Electroconvulsive Therapy Versus Sham	39
Repetitive Magnetic Stimulation Versus Sham	41
Vagus Nerve Stimulation Versus Sham.....	64
Psychotherapy Versus Control.....	65
Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Comparisons.....	68
Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Nonpharmacologic Versus Pharmacologic Treatments	69
Strength of Evidence: Tier 1 (TRD)	69
Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Key Points of Nonpharmacologic Versus Pharmacologic Treatments	70
Electroconvulsive Therapy Versus Pharmacotherapy	70
Cognitive Behavioral Therapy Versus Pharmacotherapy.....	70
Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Nonpharmacologic Versus Pharmacologic Treatments.....	70
Electroconvulsive Therapy Versus Pharmacotherapy	70
Cognitive Behavioral Therapy Versus Pharmacotherapy.....	71
Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Overview of Pharmacologic Versus Pharmacologic Treatments	74
Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Key Points of Direct Comparisons	74
Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Direct Comparisons	75
Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Overview	83
Strength of Evidence: Tier 1	84
Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Key Points	84
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation	84
Repetitive Transcranial Magnetic Stimulation Versus Sham	85
Cognitive Behavioral Therapy Versus Usual Care.....	85

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Detailed Analysis.....	85
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation.....	85
Repetitive Transcranial Magnetic Stimulation Versus Sham.....	89
Cognitive Behavioral Therapy Versus Usual Care.....	94
Key Question 3: Efficacy or Effectiveness for Treating Treatment-Resistant Depression for Particular Symptom Subtypes.....	96
Overview.....	96
Strength of Evidence: Tier 1 (TRD).....	97
Key Points.....	97
Detailed Analysis.....	97
Key Question 4: Organization of Safety, Adverse Events and Adherence.....	98
Key Question 4a: Cognitive Functioning—Overview.....	98
Strength of Evidence: Tier 1 (TRD).....	99
Key Question 4a: Cognitive Functioning—Key Points.....	100
Key Question 4a: Cognitive Functioning—Detailed Analysis.....	100
Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation.....	100
Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation.....	105
rTMS Versus Sham.....	106
Key Question 4b: Specific Adverse Events—Overview.....	108
Strength of Evidence: Tier 1 (TRD).....	109
Key Question 4b: Specific Adverse Events—Key Points.....	109
Key Question 4b: Specific Adverse Events—Detailed Analysis.....	110
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation.....	110
Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation.....	111
Repetitive Transcranial Magnetic Stimulation Versus Sham.....	112
Vagus Nerve Stimulation Versus Sham.....	115
Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Overview.....	116
Strength of Evidence: Tier 1 (TRD).....	117
Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Key Points.....	118
Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Detailed Analysis.....	118
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation.....	118
Electroconvulsive Therapy Versus Sham.....	119
Repetitive Transcranial Magnetic Stimulation Versus Sham.....	120
Vagus Nerve Stimulation Versus Sham.....	123
Cognitive Behavioral Therapy Versus Usual Care.....	124
Key Question 4d: Adherence as Measured by Overall Withdrawals—Overview.....	125
Strength of Evidence: Tier 1 (TRD).....	126
Key Question 4d: Adherence as Measured by Overall Withdrawals—Key Points.....	126
Key Question 4d: Adherence as Measured by Overall Withdrawals—Detailed Analysis.....	126

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation	127
Electroconvulsive Therapy Versus Sham	128
Repetitive Magnetic Stimulation Versus Sham	130
Cognitive Behavioral Therapy Versus Usual Care	133
Key Question 5: Efficacy and Harms for Selected Populations	134
Overview	134
Key Points	135
Detailed Analysis	136
Key Question 6: Health-Related Outcomes—Overview	139
Strength of Evidence: Tier 1 (TRD)	140
Key Question 6: Health-Related Outcomes-Key Points	141
Key Question 6: Health-Related Outcomes—Detailed Analysis	141
Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation	141
Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation	142
Repetitive Transcranial Magnetic Stimulation Versus Sham	143
Vagus Nerve Stimulation Versus Sham	144
Cognitive Behavioral Therapy Versus Control	146
Discussion	148
Background	148
Overview of Main Findings	149
KQ 1a: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Each Other in TRD Populations (Tier 1)	154
KQ 1b: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Medications in TRD Populations (Tier 1)	155
KQ 2: Efficacy of Nonpharmacologic Interventions for Maintenance of Remission or Prevention of Relapse in TRD Populations (Tier 1)	156
KQ 3: Efficacy of Nonpharmacologic Interventions for Patients with Different Symptomatology in TRD Populations (Tier 1)	156
KQ 4: Harms of Nonpharmacologic Interventions in TRD Populations (Tier 1)	157
KQ 5: Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups in TRD Populations (Tier 1)	158
KQ 6: Health-Related Outcomes of Nonpharmacologic Treatments in TRD Populations (Tier 1)	158
Applicability	159
Limitations of the Evidence Base	159
Limitations of this Review	161
Future Research	162
Conclusion	164
References	166

Tables

Table A. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for Key Question 1a, Comparative Efficacy of Nonpharmacologic Treatments	ES-4
--	------

Table B. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 1b, Comparative Efficacy of Nonpharmacologic and Pharmacologic Treatments.....	ES-5
Table C. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 2, Comparative Efficacy for Maintaining Remission.....	ES-5
Table D. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 3, Comparative Efficacy for Particular Symptom Subtypes	ES-6
Table E. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4a, Impact of Nonpharmacologic Interventions on Cognitive Functioning.....	ES-6
Table F. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4b, Specific Adverse Events.....	ES-6
Table G. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4c, Withdrawals due to Adverse Event.	ES-7
Table H. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4d, Adherence as Measured by Overall Withdrawals	ES-7
Table I. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 5, Efficacy and Harms for Selected Populations	ES-8
Table J. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 6, Health-Related Outcomes.....	ES-8
Table 1. Summary of Nonpharmacologic Interventions Covered in This Report	4
Table 2. Key Questions, Outcomes, and Study Eligibility by Key Question	13
Table 3. Relevance to TRD per CER Protocol by Tiers of Evidence Pertaining to Populations Involving Varying Proportions of Treatment-Resistant Depression.....	17
Table 4. Categories of Depressive Severity	19
Table 5. Strength of Evidence Grades and Their Definitions.....	21
Table 6. Key Questions About Treatment-Resistant Depression (TRD).....	23
Table 7. Abbreviations and Full Names of Diagnostic Scales and Other Instruments.....	27
Table 8. Number of Good- and Fair-Quality Studies by Comparison, Tier, and Diagnostic mix for KQ 1a.....	27
Table 9. Strength of Evidence: Efficacy of ECT Versus rTMS	28
Table 10. Strength of Evidence: Efficacy of ECT Plus rTMS Versus ECT	29
Table 11. Efficacy of ECT Versus rTMS: Tiers 1-3.....	30
Table 12. Efficacy of ECT Versus ECT Plus rTMS: Tiers 1-3	33
Table 13. Number of Studies Included by Comparison and Tier for KQ 1a Active Versus Control Comparisons	35
Table 14. Strength of Evidence: Efficacy of rTMS Versus Sham—Tier 1	36
Table 15. Strength of Evidence: Efficacy of VNS Versus Sham—Tier 1	37

Table 16. Efficacy of ECT Versus Sham: Tier 3	40
Table 17. Efficacy of rTMS Versus Sham: Tier 1, MDD, Augmentation Strategies	42
Table 18. Efficacy of rTMS Versus Sham: Tier 1, MDD, Mixed and Switch Strategies.....	45
Table 19. Efficacy of rTMS Versus Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder, Augmentation Strategies	48
Table 20. Efficacy of rTMS Versus Sham: Tier 2, MDD.....	55
Table 21. Efficacy of rTMS Versus Sham: Tier 2 MDD and ≤ 20 Percent Bipolar Disorder.....	57
Table 22. Efficacy of rTMS Versus Sham: Tier 3 MDD and ≤ 20 Percent Bipolar Disorder.....	58
Table 23. Efficacy of VNS Versus Sham: Tiers 1-3.....	64
Table 24. Efficacy of Psychotherapy Versus Control: Tiers 1-3	66
Table 25. Number of Good- and Fair-Quality Studies by Comparison, Tier, and Diagnostic Mix for KQ 1b	69
Table 26. Strength of Evidence: ECT Versus Pharmacotherapy	70
Table 27. Efficacy of ECT Versus Pharmacotherapy: Tier 1	71
Table 28. Efficacy of Psychotherapy Versus Pharmacotherapy: Tier 1	73
Table 29. Number of Good- and Fair-Quality Studies by Comparison and Definition of Treatment Resistance (Tier) for MDD-Only for KQ 1b.....	74
Table 30. Efficacy of Pharmacotherapy Versus Pharmacotherapy, Switching Strategies: Tier 1	76
Table 31. Efficacy of Pharmacotherapy Versus Control, Augmenting Strategies	80
Table 32. Mean Clinical Outcomes for TRD (Tier 1) Patients in Pharmacologic Studies.....	82
Table 33. Number of Studies Included by Comparison and Definition of Treatment Resistance (Tier) for KQ 2.....	83
Table 34. Strength of Evidence: Maintenance of Remission of rTMS Versus Sham – Tier 1	84
Table 35. Maintenance of Remission of ECT Versus rTMS: Tier 3, MDD	87
Table 36. Maintenance of Remission of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	88
Table 37. Maintenance of Remission of rTMS Versus Sham: Tier 1, MDD	89
Table 38. Maintenance of Remission of rTMS Versus Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder.....	90
Table 39. Maintenance of Remission of rTMS Versus Sham: Tier 2, MDD	91
Table 40. Maintenance of Remission of rTMS Versus Sham: Tier 2, MDD and ≤ 20 Percent Bipolar Disorder.....	93
Table 41. Maintenance of Remission of rTMS Versus Sham: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	94
Table 42. Maintenance of Remission of CBT Versus Usual Care: Tier 3, MDD	96
Table 43. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix for KQ 4a	99
Table 44. Strength of Evidence: Impact on Cognitive Functioning – Tier 1.....	100
Table 45. Impact on Cognitive Functioning of ECT Versus rTMS: Tier 1, MDD.....	101
Table 46. Impact on Cognitive Functioning of ECT Versus rTMS: Tier 2, MDD.....	102
Table 47. Impact on Cognitive Functioning of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	104
Table 48. Impact on Cognitive Functioning of ECT Versus ECT Plus rTMS: Tier 1, MDD	106
Table 49. Impact on Cognitive Functioning of rTMS Versus Sham: Tier 1, MDD.....	107
Table 50. Impact on Cognitive Functioning for rTMS Versus Sham: Tier 2, MDD	108

Table 51. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix That Measure Adverse Events Systematically for KQ 4b	109
Table 52. Strength of Evidence: Specific Adverse Events – Tier 1.....	110
Table 53. Adverse Events Assessed Systematically of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder	111
Table 54. Adverse Events Assessed Systematically of ECT Versus ECT Plus rTMS: Tier 1, MDD.....	112
Table 55. Adverse Events Assessed Systematically of rTMS Versus Sham: Tier 1, MDD.....	113
Table 56. Adverse Events Assessed Systematically of rTMS Versus Sham: Tier 2, MDD.....	114
Table 57. Adverse Events Assessed Systematically of rTMS Versus Sham: Tier 2, MDD and ≤ 20 Percent Bipolar Disorder	114
Table 58. Adverse Events Assessed Systematically of VNS Versus Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder	116
Table 59. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix That Assess Withdrawals Due to Adverse Events for KQ 4c	117
Table 60. Strength of Evidence: Withdrawals Due to Adverse Events -- Tier 1	117
Table 61. Withdrawals Due to Adverse Events of ECT Versus rTMS: Tier 1, MDD	118
Table 62. Withdrawals Due to Adverse Events of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	119
Table 63. Withdrawals Due to Adverse Events of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder	120
Table 64. Withdrawals Due to Adverse Events of rTMS Versus Sham: Tier 1, MDD.....	120
Table 65. Withdrawals Due to Adverse Events of rTMS Versus Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder.....	121
Table 66. Withdrawals Due to Adverse Events of rTMS Versus Sham: Tier 2, MDD.....	122
Table 67. Withdrawals Due to Adverse Events of rTMS Versus Sham: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	123
Table 68. Withdrawals Due to Adverse Events of VNS Versus Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder.....	123
Table 69. Withdrawals Due to Adverse Events of CBT Versus Sham: Tier 2, MDD.....	124
Table 70. Withdrawals Due to Adverse Events of rTMS Versus Sham: Tier 2, MDD and ≤ 20 Percent Bipolar Disorder.....	125
Table 71. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix That Assess Overall Withdrawals for KQ 4d	125
Table 72. Strength of Evidence: Overall Withdrawals During Treatment -- Tier 1	126
Table 73. Adherence/Compliance for All Comparable Interventions: All Tiers.....	127
Table 74. Overall Withdrawals of ECT Versus rTMS: Tier 1, MDD	128
Table 75. Overall Withdrawals of ECT Versus rTMS: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	129
Table 76. Withdrawals Due to Adverse Events of ECT Versus Sham: Tier 3, MDD.....	129
Table 77. Withdrawals Due to Adverse Events of ECT Versus Sham: Tier 3, MDD and ≤ 20 Percent Bipolar Disorder.....	130
Table 78. Overall Withdrawals of rTMS to Sham: Tier 1, MDD.....	130
Table 79. Overall Withdrawals of rTMS to Sham: Tier 1, MDD and ≤ 20 Percent Bipolar Disorder.....	131
Table 80. Overall Withdrawals of rTMS to Sham: Tier 2, MDD.....	132

Table 81. Overall Withdrawals of rTMS to Sham: Tier 2, MDD and \leq 20 Percent Bipolar Disorder.....	132
Table 82. Overall Withdrawals of rTMS to Sham: Tier 3, MDD and \leq 20 Percent Bipolar Disorder.....	133
Table 83. Overall Withdrawals of CBT Versus Medication: Tier 2, MDD	134
Table 84. Overall Withdrawals of CBT Versus Usual Care: Tier 2, MDD and \leq 20 Percent Bipolar Disorder.....	134
Table 85. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix of Subpopulations Presented in KQ 5.....	135
Table 86. Strength of Evidence: Efficacy and Other Comparative Clinical Outcomes of rTMS Versus Sham -- Tier 1, MDD.....	135
Table 87. Efficacy of ECT or rTMS Versus Sham for age Subpopulations: all Tiers, MDD	136
Table 88. Efficacy and Other Comparative Harms Outcomes of rTMS Versus Sham in Poststroke Depression Subpopulations: All Tiers, MDD	138
Table 89. Number of Good- and Fair-Quality Studies by TRD Tier and Diagnostic mix for KQ 6.....	140
Table 90. Strength of Evidence: Health-Related Outcome Measures – Tier 1.....	141
Table 91. Quality of Life of ECT Versus rTMS: Tier 2, MDD.....	142
Table 92. Quality of Life of ECT Versus ECT Plus rTMS: Tier 1, MDD	143
Table 93. Quality of Life of rTMS Versus Sham: Tier 1, MDD And \leq 20 Percent Bipolar Disorder.....	144
Table 94. Quality of Life of rTMS Versus Sham: Tier 2, MDD and \leq 20 Percent Bipolar Disorder.....	145
Table 95. Quality of Life of VNS Versus Sham: Tier 1, MDD and \leq 20 Percent Bipolar Disorder.....	145
Table 96. Quality of Life of CBT Versus Control: Tier 2, MDD.....	146
Table 97. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for Key Question 1a. Comparative Efficacy of Nonpharmacologic Treatments.....	149
Table 98. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 1b. Comparative Efficacy of Nonpharmacologic and Pharmacologic Treatments.....	151
Table 99. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 2. Comparative Efficacy for Maintaining Remission.....	151
Table 100. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 3. Comparative Efficacy for Particular Symptom Subtypes	151
Table 101. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4a. Impact of Nonpharmacologic Interventions on Cognitive Functioning.....	152
Table 102. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4b. Specific Adverse Events.....	152

Table 103. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4c. Withdrawals Due To Adverse Event	153
Table 104. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 4d. Adherence as Measured by Overall Withdrawals	153
Table 105. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 5. Efficacy and Harms for Selected Populations	153
Table 106. Summary of Findings on Nonpharmacologic Treatment of Adult Treatment-Resistant Depression (TRD) With Strength of Evidence for Tier 1 (TRD) for KQ 6. Health-Related Outcomes.....	154
Table 107. Number of Tier 1 (TRD) Studies of Head-To-Head Comparisons of Nonpharmacologic Treatments, by Comparison	154
Table 108. Number of Tier 1 (TRD) Studies of Nonpharmacologic Interventions Against Controls or Usual Care, by Comparison	155
Table 109. Number of Tier 1 (TRD) Studies Involving Pharmacotherapy, by Comparison.....	155

Figures

Figure 1. Phases of Treatment for Major Depression With Response to Initial Treatment.....	1
Figure 2. Phases of Treatment for Resistant Depression (Treatment Refractory).....	2
Figure 3. Analytic Framework for Nonpharmacologic Interventions for Treatment-Resistant Depression	12
Figure 4. PRISMA Tree/Disposition of Articles	25
Figure 5. Mean Difference Meta-analysis of Changes in Depressive Severity Comparing rTMS With Sham: Tier 1, MDD.....	47
Figure 6. Relative Risk Meta-analysis of Response Rates Comparing rTMS With Sham: Tier 1, MDD	47
Figure 7. Relative Risk Meta-analysis of Remission Rates Comparing rTMS With Sham: Tier 1, MDD	48
Figure 8. Relative Risk Meta-analysis of Response Rates Comparing rTMS Versus Sham: Tier 1, MDD/ \leq 20 Percent Bipolar Disorder	51
Figure 9. Mean Difference Meta-analysis of Changes in Depressive Severity Comparing rTMS Versus Sham: Tier 1	52
Figure 10. Relative Risk Meta-analysis of Response Rates Comparing rTMS Versus Sham: Tier 1.....	53
Figure 11. Relative Risk Meta-analysis of Remission Rates Comparing rTMS Versus Sham: Tier 1.....	53
Figure 12. Mean Difference Meta-analysis of Changes in Depressive Severity Comparing rTMS With Sham: Tiers 1 & 2, MDD.....	60
Figure 13. Relative Risk Meta-analysis of Response Rates Comparing rTMS With Sham: Tiers 1 & 2, MDD.....	61
Figure 14. Relative Risk Meta-analysis of Remission Rates Comparing rTMS With Sham: Tiers 1 & 2, MDD.....	61
Figure 15. Relative Risk Meta-analysis of Response Rates Comparing rTMS With Sham: Tiers 1 & 2, MDD/ \leq 20 Percent Bipolar Disorder	62

Figure 16. Relative Risk Meta-analysis of Response Rates Comparing rTMS With Sham: Tiers 1 & 2, All Populations	63
Figure 17. Relative Risk Meta-analysis of Remission Rates Comparing rTMS With Sham: Tiers 1 & 2, All Populations	63

Appendixes

Appendix A. Search Strategy	
Appendix B. Data Abstraction Forms	
Appendix C. Excluded Studies	
Appendix D. Evidence Tables	
Appendix E. Abbreviations and Full Names of Diagnostic Scales and Other Instruments	
Appendix F. Characteristics of Studies With Poor Internal Validity	
Appendix G. Articles by Database Searched	
Appendix H. Studies Recommended for Inclusion by Peer and Public Reviewers	

Executive Summary

Background

Major depressive disorder (MDD) is common and costly. Over the course of a year, between 13.1 million and 14.2 million people will experience MDD. Approximately half of these people seek help for this condition, and only 20 percent of those receive adequate treatment. For those who do initiate treatment for their depression, approximately 50 percent will not adequately respond following acute-phase treatment; this refractory group has considerable clinical and research interest. Patients with only one prior treatment failure are sometimes included in this group, but patients with two or more prior treatment failures are a particularly important and poorly understood group and are considered to have treatment-resistant depression (TRD). These TRD patients represent a complex population with a disease that is difficult to manage.

Patients with TRD incur the highest direct and indirect medical costs among those with MDD. These costs increase with the severity of TRD. Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than six times the mean total costs of depressed patients who are not treatment resistant. After considering both medical and disability claims from an employer's perspective, one study found that TRD employees cost \$14,490 per employee per year, whereas the cost for non-TRD employees was \$6,665 per employee per year.

Given the burden of TRD generally, the uncertain prognosis of the disorder, and the high costs of therapy, clinicians and patients alike need clear evidence to guide their treatment decisions. The choices are wide ranging, include both pharmacologic and nonpharmacologic interventions, and are fraught with incomplete, potentially conflicting evidence. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for patients with TRD. Antidepressant medications, which are the most commonly used intervention, have decreasing efficacy for producing remission after patients have experienced two treatment failures. Such drugs also often have side effects, sometimes minor but sometimes quite serious. For these reasons, clinicians often look for alternative strategies for their TRD patients.

This review from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center (EPC) provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments as therapies for patients with TRD: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT).

The core patient population of interest was patients with MDD who met our definition of TRD: failure to respond following two or more adequate antidepressant treatments. We also included TRD studies in which the patient population could include a “mix” of up to 20 percent of patients with bipolar disorder (i.e., 80 percent or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations.

We structured our review to maintain our focus on study populations meeting our TRD definition (≥ 2 antidepressant failures) while not excluding potentially relevant evidence. We identified different tiers of TRD-related studies to use in our analytic strategy:

- **Tier 1** Evidence (TRD as defined in this report): studies in which patients specifically had two or more prior treatment failures with medications.
- **Tier 2** Evidence: studies in which patients had one or more prior treatment failures.
- **Tier 3** Evidence: studies in which the number of prior failed treatments was not specified but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures; these data have probable relevance to TRD. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

This comparative effectiveness review is intended to help various decisionmakers come to informed choices about the use of nonpharmacologic interventions for TRD in adults. Our principal goal is to summarize comparative data on the efficacy, effectiveness, and harms of ECT, rTMS, VNS, and CBT/IPT in patients with TRD. Comparisons of these nonpharmacologic therapies are our main interest. However, because treatment decisions made by patients with TRD and their clinicians are not limited to nonpharmacologic options, we also compare nonpharmacologic options with pharmacologic ones. We address the following six Key Questions (KQs) as specified by the Agency for Healthcare Research and Quality (AHRQ).

“Trials” in these KQs refers to treatment attempts, not experimental studies.

- KQ 1a. For adults with TRD (defined as two or more failed adequate trials of a biologic [i.e., pharmacologic] intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- KQ 1b. How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?
- KQ 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?
- KQ 3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?
- KQ 4. For adults with TRD, do nonpharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.
- KQ 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations:
 - Elderly or very elderly patients; other demographic groups (defined by age, ethnic or racial groups, and sex)?
 - Patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer)?
- KQ 6. For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

We searched MEDLINE, Embase, the Cochrane Library, PsycINFO, and International Pharmaceutical Abstracts. We searched for systematic reviews, clinical controlled trials, meta-analyses, and nonexperimental studies in which the investigator did not assign group allocation. Sources were searched from 1980 through November 18, 2010. AHRQ Scientific Resource Center (SRC) staff contacted device manufacturers and invited them to submit dossiers, including citations. The SRC also provided our EPC with other relevant data that may not have been captured in the literature search.

For efficacy and effectiveness (KQs 1 and 2), we first focused on head-to-head randomized controlled trials (RCTs) comparing one intervention with another. When sufficient head-to-head evidence was unavailable, we evaluated indirect evidence: nonpharmacologic interventions versus placebo- or sham-controlled evidence or “treatment as usual” controls. For KQs 3, 4, 5, and 6, we examined data from both experimental and observational studies (generally prospective cohort studies). We did not formally distinguish efficacy from effectiveness trials.

We rated the quality of individual studies as good, fair, or poor; only good or fair studies are included in these analyses. We evaluated the strength of the various bodies of evidence using principles stated in the AHRQ Methods Guide for Comparative Effectiveness Reviews, which grades strength as high, moderate, low, or insufficient. We evaluated the applicability of the body of evidence using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting.

Throughout this report we synthesized the literature qualitatively. If data were sufficient, we conducted meta-analyses of data for comparisons involving trials that were fairly homogenous in study populations, treatment intervention, and outcome assessments. Given our focus on Tier 1 (TRD) studies, for each KQ we first present an overview of the particular comparison, including the strength of evidence findings for the Tier 1 studies. This summary does not present detailed findings from the Tier 2 and Tier 3 studies. The results chapter of the full report presents those data in greater detail.

Results: Overview

From a total of 2,754 citations retrieved, we ultimately identified 79 good-, fair-, or poor-quality articles in this review; they represent 64 studies. Of these studies, there were 17 head-to-head RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a nonpharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTs of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RCTs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). We excluded 8 studies (8 articles) because of poor quality. We present evidence that allows comparison of the four nonpharmacologic treatments of interest (ECT, rTMS, VNS, and psychotherapy) stratified by tiers of evidence.

Comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy. Many clinical questions about efficacy and effectiveness remain unanswered. The text below presents our principal results; summary tables (A–J) document Tier 1 TRD findings for major comparisons and outcomes for each key question, give the overall strength of evidence for that comparison, and outline key findings. We report first on direct evidence (head-to-head comparisons) and then on indirect evidence (e.g., trials using controls). If a specific comparison did not involve a Tier 1 population but did have trials conducted in a Tier 2 and/or Tier 3

population, we have listed it in this table, noted “No eligible studies identified,” and added a footnote indicating the presence of at least one such study.

The greatest volume of evidence is for ECT and rTMS; however, the direct comparative evidence about even these treatments is quite limited. Available indirect evidence primarily involves rTMS; a little information is available on VNS and psychotherapy (chiefly for efficacy and adverse events), and no available indirect evidence involves ECT. Given the limited number of Tier 1 studies incomplete reporting on the number of failed treatment attempts, we were unable to stratify our outcomes by the number of treatment failures within Tier 1.

Table A. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a, comparative efficacy of nonpharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
ECT vs. rTMS	Change in depressive severity	42	Low	1 fair trial: both ECT and rTMS improved symptom severity but did not differ significantly.
ECT vs. rTMS	Response rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT vs. rTMS	Remission rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT plus rTMS vs. ECT	Change in depressive severity	22	Low	1 fair trial: both ECT and ECT plus rTMS improved symptom severity but did not differ significantly.
ECT plus rTMS vs. ECT	Response rate	0	NA	No eligible studies identified. [‡]
ECT plus rTMS vs. ECT	Remission rate	22	Low	1 fair trial: ECT and ECT plus rTMS did not differ significantly.
ECT vs. sham	Change in depressive severity	0	NA	No eligible studies identified. [‡]
ECT vs. sham	Response rate	0	NA	No eligible studies identified. [‡]
ECT vs. sham	Remission rate	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Change in depressive severity	497	High	7 trials (3 good, 4 fair): rTMS had a significantly greater decrease in depressive severity than sham. 4 fair trials: rTMS had nonsignificantly greater decrease in depressive severity than sham. 2 fair trials: rTMS had greater decrease than sham but significance NR. 1 fair trial: rTMS did not significantly differ from sham.
rTMS vs. sham	Response rate	471	High	4 trials (3 good, 1 fair): rTMS had a significantly higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly higher response rate than sham. 6 fair trials: rTMS had a higher response rate than sham, but significance NR. 1 fair trial: rTMS did not clearly differ from sham, but significance NR.
rTMS vs. sham	Remission rate	223	Moderate	3 trials (2 good, 1 fair): rTMS had significantly greater remission rate than sham. 1 fair trial: rTMS had a greater remission rate than sham but significance NR.
VNS vs. sham	Change in depressive severity	235	Low	1 good trial: VNS and sham did not differ significantly.
VNS vs. sham	Response rate	235	Low	1 good trial: VNS and sham did not differ significantly.
Psychotherapy vs. control	Change in depressive severity	0	NA	No eligible studies identified. [‡]

Table A. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a, comparative efficacy of nonpharmacologic treatments (continued)

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
Psychotherapy vs. control	Response rate	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. control	Remission rate	0	NA	No eligible studies identified. [‡]

ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 or Tier 3 study addressed this comparison.

Table B. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 1b, comparative efficacy of nonpharmacologic and pharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
ECT vs. pharmacotherapy	Change in depressive severity	39	Low	1 fair trial: ECT had significantly greater improvement in symptom severity than pharmacotherapy.
ECT vs. pharmacotherapy	Response rate	39	Low	1 fair trial: ECT had significantly greater response rates than pharmacotherapy.
Psychotherapy vs. pharmacotherapy	Change in depressive severity	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. pharmacotherapy	Response rate	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. pharmacotherapy	Remission rate	0	NA	No eligible studies identified. [‡]

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table C. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 2, comparative efficacy for maintaining remission

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
ECT vs. rTMS	Maintenance of remission	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Maintenance of remission	68	Insufficient	3 fair trials: no significant differences in maintenance of remission; however, small sample sizes in two of the studies and the presence of a co-intervention in the third study make results difficult to interpret.
CBT vs. usual care	Maintenance of remission	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table D. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 3, comparative efficacy for particular symptom subtypes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	0	NA	No eligible studies identified. ‡

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table E. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4a, impact of nonpharmacologic interventions on cognitive functioning

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Cognitive functioning	72	Insufficient	1 fair trial and 1 fair cohort study: Some evidence suggests no difference between treatments, whereas some evidence suggests ECT may have deleterious impact on cognitive functioning compared with rTMS (1 study: significant effect on 1-week recall; both studies: nonsignificant effect on all other measures).
ECT vs. ECT + rTMS	Cognitive functioning	22	Insufficient	1 fair trial: no significant differences in a single item measure on memory problems.
rTMS vs. sham	Cognitive functioning	161	Insufficient	4 trials (1 good, 3 fair): Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham (2 trials: significant differences in memory, verbal fluency; all other findings nonsignificant or significance not reported).

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

Table F. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4b, specific adverse events

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Adverse events	0	NA	No eligible studies identified. ‡
ECT vs. ECT + rTMS	Adverse events	22	Low	1 fair trial: no significant differences in specific adverse events
rTMS vs. sham	Adverse events	68	Low	1 good trial: rTMS resulted in significantly more scalp pain at the stimulation site than sham.
VNS vs. sham	Adverse events	235	Low	1 fair trial: Some differences in specific adverse events reported ($P = NR$)

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table G. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4c, withdrawals due to adverse event

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Withdrawals	30	Low	1 fair cohort study: no difference in withdrawals between ECT and rTMS groups ($P = NR$).
ECT vs. sham	Withdrawals	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Withdrawals	337	Insufficient	7 trials (1 good, 6 fair): trials showed mixed results about withdrawals attributed to adverse events.
VNS vs. sham	Withdrawals	235	Low	1 good trial: VNS had greater withdrawals attributed to adverse events than sham (significance NR).
CBT vs. usual care	Withdrawals	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table H. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4d, adherence as measured by overall withdrawals

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Overall withdrawals	72	Low	1 fair trial and 1 fair cohort study: studies showed more withdrawals in the ECT group compared with rTMS ($P = NR$).
ECT vs. sham	Overall withdrawals	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Overall withdrawals	325	Insufficient	8 fair trials: trials showed mixed results about withdrawals.
CBT vs. usual care	Overall withdrawals	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table I. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 5, efficacy and harms for selected populations

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
rTMS vs. sham	Changes in depressive severity	34	Low	1 fair trial: rTMS produced better outcome than sham in young adult population (ages 18–37).
rTMS vs. sham	Changes in depressive severity	20	Low	1 fair trial: rTMS produced better outcome than sham in older adults with post-stroke depression.
rTMS vs. sham	Response	34	Low	1 fair trial: rTMS produces better response rates than sham in young adult population (ages 18–37).
rTMS vs. sham	Response	20	Low	1 fair trial: no difference between rTMS and sham for older adults with post-stroke depression.
rTMS vs. sham	Remission	20	Low	1 fair trial: no difference between rTMS and sham in older adults with post-stroke depression.

rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

Table J. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 6, health-related outcomes

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. ECT + rTMS	Health-related outcomes	22	Low	1 fair trial: There were no differences between groups in improvements in daily functioning.
rTMS vs. sham	Health-related outcomes	60	Low	1 fair trial: low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham.
VNS vs. sham	Health-related outcomes	214	Low	1 fair trial: VNS and sham groups did not differ significantly in daily functioning.
CBT/DBT vs. control	Health-related outcomes	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on the on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Efficacy of Nonpharmacologic Interventions Against Other Nonpharmacologic Interventions (KQ 1a)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD is limited to two fair trials (both in MDD-only populations). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of psychotherapy with another nonpharmacologic intervention.

Indirect Evidence

We identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS, or psychotherapy, with a control or sham procedure in Tier 1 populations. We identified no eligible ECT versus control studies. The number of these trials with the same or similar control group was very small, so we could not pool them quantitatively. We could, however, assess the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than three times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than six times as likely to achieve remission as those receiving the sham.

In the only other Tier 1 comparison, one good-quality VNS versus sham control trial (a mixed MDD/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

Efficacy of Nonpharmacologic Interventions Compared With Antidepressant Pharmacotherapies (KQ 1b)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) for Tier 1 trials is limited to one fair trial (a mixed MDD/bipolar population). ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71 percent vs. 28 percent) than medications (low strength of evidence).

Indirect Evidence

Indirect evidence about procedures or psychotherapy (vs. sham or nonpharmacologic controls) was presented above as part of KQ 1.

We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, we found no comparable, common control groups (i.e., patients not receiving a mood-related medication) to allow such comparisons.

Instead, we determined mean average outcomes for pharmacologic treatments.

- For switching strategies, mean pharmacologic response rates averaged 39.8 percent (95% CI, 30.7% to 48.9%) and mean remission rates averaged 22.3 percent (95% CI, 16.2% to 28.4%).
- For augmentation, mean response rates averaged 38.1 percent (31.0% to 45.3%) and mean remission rates averaged 27.2 percent (20.4% to 34.0%).
- For maintenance strategies, mean response rates averaged 27.3 percent (19.8% to 34.8%) and mean remission rates averaged 16.8 percent (13.5% to 20.2%).

Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should be compared to nonpharmacologic outcomes only with caution.

Maintenance of Remission or Prevention of Relapse (KQ 2)

Direct Evidence

With respect to maintaining remission (or preventing relapse), we had no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence

Three fair trials compared rTMS with a sham procedure and found no significant differences. However, too few patients were followed during the relapse prevention phases in two of the three studies, and patients in the third received a co-intervention providing insufficient evidence for a conclusion. We had no eligible studies for ECT, VNS, or psychotherapy.

Efficacy of Nonpharmacologic Interventions for Patients With Different Symptomatology (KQ 3)

Direct Evidence

We identified no Tier 1 trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

Indirect Evidence

We identified no studies testing either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

Safety, Adverse Events, and Adherence (KQ 4)

Direct Evidence

In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients. However, the data were insufficient to reach a conclusive result. For just this set of analyses, we examined both clinical trials and cohort studies, and we focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

Cognitive Functioning

For Tier 1 studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence). No differences between groups on a single-item measure of cognitive functioning were found in a study comparing ECT with ECT and rTMS (insufficient strength of evidence).

Specific Adverse Events

One Tier 1 study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence).

Withdrawals

We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).

Evidence for ECT compared with rTMS indicated higher rates of overall withdrawals in the ECT compared to the rTMS group ($P = \text{NR}$; low strength of evidence).

Indirect Evidence

We attempted to include data from the same types of studies and for the same outcomes as for direct evidence. We identified no studies comparing ECT versus control.

Cognitive Functioning

Mixed evidence on cognitive functioning in rTMS versus sham was insufficient evidence to draw a conclusion (insufficient strength of evidence).

Specific Adverse Events

rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence).

Some differences in the frequency of specific adverse events were seen when comparing VNS and sham groups, but the significance of the findings was not reported ($P = \text{NR}$) (low strength of evidence).

Withdrawals

Findings were mixed in Tier 1 studies as to whether rTMS groups had greater rates of withdrawals (overall and due to adverse events) than groups receiving sham procedures (insufficient evidence for both).

Withdrawals attributable to adverse events were higher in the VNS group compared with sham (low strength of evidence).

No Tier 1 studies reported on withdrawals for CBT groups versus those receiving some form of usual care.

Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups (KQ 5)

Direct Evidence

We found no studies (in any tier) directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

Indirect Evidence

Two Tier 1 trials compared rTMS with sham. All findings provided low strength of evidence. For young adults (ages 18–37), one trial found that rTMS produced a greater decrease in depressive severity and a greater response rate than sham. A second trial, conducted in older adults with post-stroke depression, found that rTMS produced a greater decrease in depressive severity and a greater response rate but no difference in remission rates compared with a sham control.

Health-Related Outcomes of Nonpharmacologic Treatments (KQ 6)

Direct Evidence

With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

Indirect Evidence

Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

Applicability

For the limited amount and low strength of evidence available, the data for Tier 1 (TRD) is generally applicable to TRD populations. Populations enrolled in these trials appeared representative of our target population. Studied interventions were comparable to those in routine use, though dose and duration of nonpharmacologic treatment often varied between studies.

Measured outcomes on the whole reflected the most important clinical outcomes for depression measures, although reporting was inconsistent; outcomes for the other key questions were much more restricted. Followup periods were generally shorter than desirable, but most

were sufficient to measure an initial acute-phase treatment response. Study settings were a mixture of inpatient and outpatient, because ECT is generally an inpatient procedure and the others are generally outpatient. Some evidence highlights the importance of patient acceptability of treatment as some patients refuse particular interventions. An individualized balance between a patient's needs and concerns must be taken into account during selection from a range of nonpharmacologic and pharmacologic antidepressant treatment options.

The use of inconsistent definitions of TRD in the trials and the absence of analyses considering the effect of the number of current treatment failures on outcomes hindered interpretation of data, leading to our use of a tiered system for analyses. The evidence base combining data for Tiers 1–3 on the whole produced findings that were consistent with Tier 1 TRD data and also appear applicable to TRD populations.

Remaining Issues

This area of comparative clinical research is in its infancy. Key areas for future research need primarily to lay more robust foundations for an evidence base that can better inform decisions for clinicians and patients.

The Field Needs a Standard Definition of TRD That Investigators Should use in Their Clinical Trials Research

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by the variability in TRD definitions. Although these definitions appear to be converging on a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it.

Progress in this area of research requires better standardization of this concept, so that future reviews of the evidence do not need to resort to differentiating, as we did, between “Tier 1” studies (i.e., TRD by this definition based on two or more treatment failures) and “Tier 2 or 3” types of studies. The latter do provide information that helps illuminate likely impacts of these interventions on patients with TRD, but that is not the same thing as having robust studies focused clearly on the patient population of greatest interest. The challenge will be to provide a definition that operationalizes TRD to make it feasible for clinicians while at the same time successfully capturing the complexity of treatment resistance.

More Clinical Trials, as Well as Other Possible Study Designs, That Compare Nonpharmacologic Interventions With Other Nonpharmacologic Options and With Pharmacologic Treatments are Necessary to Inform Decisionmaking in TRD

Clinicians, patients, and policymakers need additional relevant data to guide difficult treatment decisions about what to do next: try another medication (and should it be an augmentation, switch, or combination strategy?) or add (or switch to) rTMS, ECT, VNS, or psychotherapy?

Also, given that treatment options for many TRD patients include medications, trials should directly compare nonpharmacologic interventions with each other and with pharmacologic treatments.

The Number of Treatment Failures in the Current Episode Should be Delineated Carefully

This information, more likely to be accurate than lifetime histories of failures, can help investigators determine whether the particular number of failures, or reaching a particular number of failures in a current episode, can help differentiate between nonpharmacologic treatment choices. For example, for patients with two treatment failures in a current episode, the outcomes may not differ between cognitive therapy and rTMS; however, for patients with a different (higher or lower) number of treatment failures in the current episode, one nonpharmacologic treatment may indeed be better than the other. Currently, we do not know what the proper threshold is for selection of treatment. Clarification of the scientific basis for such a decision would substantially improve decisionmaking.

Clarifying Whether Responses Differ for TRD Patients With MDD Compared With Those With Bipolar Disorder Will Help Guide Future Clinical Trial Design

Our decision to include trials with patient populations including up to 20 percent with bipolar disorder (i.e., the “mixed” populations noted earlier) was guided by clinical experience and common sense but not by data. Testing to see whether outcomes differ between the two groups can yield information about inclusion criteria (should the mix be 0 percent, 10 percent, 20 percent, etc.?) that may be useful to investigators in designing TRD trials and may be important to consider as a potential covariate in analyses involving such mixes.

Greater Consideration Should be Given to the Role That the Spectrum of Depressive Severity Plays

Using a finer gradation of depressive severity than investigators now typically employ might identify whether particularly severe degrees of depression, most commonly understood currently as a $\text{HAM-D}_{17} \geq 20$, may respond differently to the available nonpharmacologic interventions than do less severe levels of depression. These gradations may lead clinicians to a better understanding of severe depression and its role in guiding treatment selection in TRD.

Direct Comparisons of Treatment Strategies, Holding Consistent any Coexisting or Concomitant Therapies, are Imperative

Decisionmakers need to know whether outcomes with nonpharmacologic treatments are better when such a treatment augments the current treatment, replaces the current treatment, or replaces the current treatment in combination with another treatment. When ongoing treatment is uncontrolled and reflects a variety of treatments—e.g., some patients continue with atypical antipsychotics, some with mood stabilizers, some with no psychotropic medications—results of such studies are difficult, if not impossible, to interpret.

Consistent Reporting of Changes in Depressive Severity, Response Rates, and Remission Rates is Crucial

To allow for better comparisons of clinical outcomes in this difficult-to-treat population, all three measures offer useful information for clinicians. Thus, for either clinical trials or observational studies, investigators should attempt to collect data on all three routinely.

Application of Consistent, Accepted Protocols in Trials is Necessary

Making sure that patients receive equivalent doses of different nonpharmacologic interventions is more difficult than making sure of this for pharmacologic interventions. Nevertheless, investigators designing trials of nonpharmacologic therapies can attempt to do so by implementing standard accepted protocols for their trials. Such “dosing” had been difficult to control when that protocol was in the process of being developed, as with rTMS, but given current treatment parameters, this standardization is a goal well worth trying to reach.

More Careful and Consistent Assessment of Adverse Events is Required

Adverse event reporting is quite limited and tends to cover only a short time span; what reporting does exist is variable and inconsistent. Systematic collection and more consistent reporting of data on harms—that is, adverse events and negative side effects—and information about attrition and withdrawal would provide useful information to help balance information now focused on clinical benefits. Use of the CONSORT statement (available at: <http://www.consort-statement.org/home/>), which guides proper reporting of study information (including the presentation of adverse events), would strengthen reporting of both harms and other clinical trial findings; it would also aid in the critical appraisal and interpretation of all study results. Further, a more informative assessment of adverse events would require studies to be able to assess long-term and cumulative outcomes.

Including Key Relevant Measures and Subgroups in Subsequent Research is Desirable

As indicated by the review, nearly no evidence exists on how the effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristic (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression; perinatal depression). Also essentially missing is information about health-related outcomes, especially those reported by patients, that concern their quality of life or levels of functional impairment. Subsequent studies should focus on employing known, reliable, and valid measures of patient-reported outcomes, such as the MOS SF-36, the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q), and the EQ-5D.

Including Comparisons of Newer Nonpharmacologic Interventions Will be Important in Future Research

As new nonpharmacologic treatments are developed and tested, investigators should try to include them as potential comparators. At the time we started this comparative effectiveness

review, clinical trial data on some of the developing nonpharmacologic interventions, such as magnetic seizure therapy or deep brain stimulation, were insufficient (from the published literature) for us to try to include them. As the evidence bases grow to support the efficacy of such additional nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs.

Conclusion

Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is early in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS. However, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for benefits, reflecting low confidence that the evidence reflects the true effect and indicating that further research is likely to change our confidence in these findings. This finding of low strength is most notable in two cases: ECT and rTMS did not produce different clinical outcomes in TRD, and ECT produced better outcomes than pharmacotherapy. No trials directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions with themselves and with pharmacologic treatments, and to delineate carefully the number of treatment failures following a treatment attempt of adequate dose and duration in the current episode.

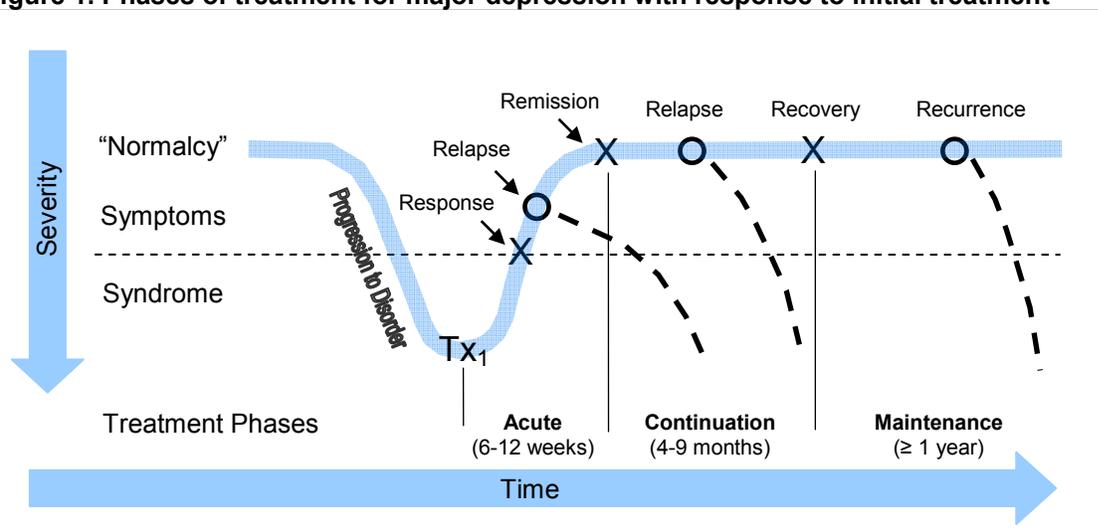
Introduction

Burden and Costs of Disease

Major depressive disorder (MDD) is common and costly. Over the course of a year, between 13.1 million and 14.2 million people will experience MDD.¹ Approximately half of these people seek help for this condition, and only 20 percent of those receive adequate treatment.²

Among people who do receive adequate treatment, the normal course of treatment consists of an acute phase lasting 6 to 12 weeks with the goal of remission, meaning a complete resolution of the depressive episode (Figure 1). This is followed by a continuation phase of treatment during which the treatment goal is continued absence of depressive symptoms (i.e., relapse prevention) for an additional 4 to 9 months such that the patient's episode can be considered completely resolved. A maintenance phase lasting an additional 1 or more years is recommended in patients who have had two or more previous episodes of depression to prevent the recurrence of a new depressive episode.^{3,4}

Figure 1. Phases of treatment for major depression with response to initial treatment



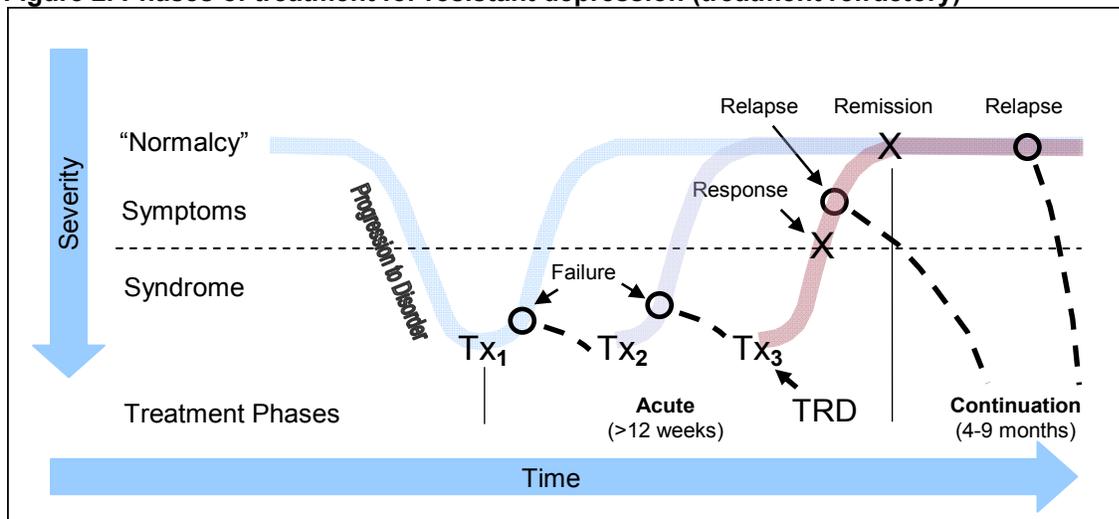
Source: Re-created based on Kupfer, 1991.⁵ Tx₁ = treatment attempt 1. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Unfortunately, the course of treating patients with depression (especially MDD) often does not follow the idealized treatment phases of reaching, continuing, and maintaining remission as depicted in Figure 1. In the acute phase of treatment, only 30 percent of patients reach the treatment goal of remission. The remaining 70 percent will either obtain response (usually defined as at least a 50 percent reduction in depressive severity) without remitting (about 20 percent) or not respond at all (50 percent).⁶

This 50 percent of people whose depressive disorder does not adequately respond following acute-phase treatment appear to have a harder-to-treat depression,⁷ and this refractory group has generated considerable clinical and research interest.⁷ Patients with only one prior treatment failure are sometimes included in this group, but patients with two or more prior failed treatment attempts are a particularly important and poorly understood group⁸ and are considered to have

treatment-resistant depression (TRD; see the section below on patient populations included) (Figure 2).⁸ Indeed, for patients whose depression does not remit after two adequate treatment attempts in the current episode, the likelihood of recovery with subsequent medication treatment decreases by half to approximately 15 percent.⁸ In contrast with Figure 1, which depicts the course of treatment for a patient responding to first-line treatment (i.e., Tx₁), the treatment-resistant patients depicted in Figure 2 require additional treatments (i.e., Tx₂, Tx₃, or more) and thus have prolonged depressive symptoms during unsuccessful acute phase treatment. Patients with two or more treatment failures during the same depressive episode (i.e., those marked as having TRD at Tx₃ in the figure) are also believed to have more resistant disease than patients with two or more prior treatment failures during their entire lifetime. The former group of patients seemingly has a more uncertain prognosis for their condition over time than do patients not seen as treatment-resistant (as defined here); by extension, they face longstanding and greater burden of disease.

Figure 2. Phases of treatment for resistant depression (treatment refractory)



Source: Adopted from Kupfer, 1991⁵ Tx₁₋₃ = Treatment attempt 1, 2, and 3, respectively; TRD = treatment-resistant depression. Dashed lines indicate hypothetical worsening of depressive severity, which could indicate failure of treatment, relapse, or recurrence.

Although TRD broadly is defined as inadequate response following adequate antidepressant therapy in MDD, treatment resistance is a complex phenomenon that is influenced by heterogeneity in depressive subtypes, psychiatric comorbidity, and comorbid medical illnesses.⁹ As described in Figure 2, major depression is usually considered treatment resistant when at least two antidepressant attempts have failed.¹⁰ However, criteria for treatment resistance have been variably defined in clinical research and practice. Important factors related to the definition of TRD include the number of failed treatments, the time between treatment attempts, and the adequacy of the dose and duration of antidepressant treatment. The term “pseudo-resistance” has been used to describe patients classified as treatment resistant even though they never actually received an adequate treatment course; pseudo-resistance may account for as many as 60 percent of patients initially classified as TRD.⁹

Patients with TRD incur the highest direct and indirect medical costs among those with MDD. These costs increase with the severity of TRD.¹¹ Treatment-resistant patients are twice as likely to be hospitalized, and their cost of hospitalization is more than six times the mean total

costs of depressed patients who are not treatment resistant.¹² After considering both medical and disability claims from an employer's perspective, one study found that TRD employees cost \$14,490 per employee per year, whereas the cost for non-TRD employees was \$6,665 per employee per year (1996–1998).¹³

Purpose of This Report

Given the burden of TRD generally, the uncertain prognosis of the disorder, and the high costs of therapy, clinicians and patients need clear evidence to guide their treatment decisions. The choices are wide ranging, include both pharmacologic and nonpharmacologic interventions, and are fraught with incomplete, potentially even conflicting, evidence. Somatic treatments, which may involve use of a pharmacologic intervention or a device, are commonly considered for patients with TRD. Antidepressant medications, which are the most commonly used intervention, have decreasing efficacy for producing remission after patients have experienced two failures. Such drugs also often have side effects,⁸ sometimes minor but sometimes quite serious.¹⁴ For these reasons, clinicians often look for alternative strategies for their TRD patients.

This comparative effectiveness review (CER) is intended to help various decisionmakers come to informed choices about the use of nonpharmacologic interventions for TRD in adults. Our principal goal is to summarize comparative data on the efficacy, effectiveness, and harms of electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy (CBT) or interpersonal psychotherapy (IPT) in patients with TRD. Comparisons between two or more nonpharmacologic interventions are our main interest; however, because patients with TRD and their clinicians often decide between another medication treatment and a nonpharmacologic option, we also compare nonpharmacologic options with pharmacologic ones, both directly and indirectly. The goal is to produce a rough estimate of how these strategies compare for this patient population.

Included Interventions

Nonpharmacologic somatic treatments and nonsomatic psychotherapy treatments offer alternatives to antidepressant medications, although the evidence base for many of these treatments is limited. At the time the protocol for this review was developed, only four types of interventions had an evidence base sufficient to establish their efficacy and therefore be considered appropriate for a CER. Interventions that offer promising options for patients with TRD include ECT, rTMS, VNS, and evidence-based psychotherapy (e.g., cognitive therapy, such as cognitive behavioral therapy [CBT or IPT]). In some cases, these therapies or procedures can be used in combination (e.g., ECT and rTMS). Table 1 provides a summary of these principal nonpharmacologic interventions, including their uses, technical parameters, common side effects, and contraindications. They are described in more detail below. Generally, although these interventions may be safe and effective options for TRD, little evidence exists to guide decisions about their comparative efficacy. Further, how the nonpharmacologic options compare with pharmacologic treatments remains unclear.

Electroconvulsive Therapy (ECT)

ECT has been available for use in the United States since the 1930s. Current evidence indicates that ECT has a role in the treatment of people with depression and in certain subgroups

of people with schizophrenia, catatonia, and mania.^{15,16} Its primary current role in depression is for treatment resistance or intolerance.¹⁷ Because ECT was introduced prior to U.S. Food and Drug Administration (FDA) device regulation, it was not subjected to formal review and approval as a device. It has since been classified as a class III device, which means that

Table 1. Summary of nonpharmacologic interventions covered in this report

Major Factors About Nonpharmacologic Interventions	Electroconvulsive Therapy (ECT)	Repetitive Transcranial Magnetic Stimulation (rTMS)	Vagus Nerve Stimulation (VNS)	Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT)
Description	Passing an electric current through the brain after administering anesthetic and muscle relaxants, to produce a convulsion	Focal magnetic stimulation through the scalp without the use of anesthesia ¹⁸	Surgically placed electrodes around the left vagus nerve to modulate mood and control seizures	Psychotherapy to identify negative depressogenic cognitions ¹⁹ or interpersonal behaviors ²⁰
Uses	Depression, schizophrenia, catatonia, mania	Depression, mania, anxiety, schizophrenia, epilepsy, Parkinson's disease ²¹	Depression, epilepsy	Depression, bipolar disorder, psychosis, anxiety, personality disorders, eating disorders
Common Placement Sites	Bifrontal/bilateral or unilateral electrode placement	Dorsolateral prefrontal cortex	Left vagus nerve	Not applicable
Average Duration	Administered 2 or 3 times a week for 3-4 weeks ²²	40 minutes daily (usually weekdays) for 2-6 weeks ²³	30 seconds every 5 minutes, generally for 10 weeks ²⁴	Weekly sessions for 3-4 months
Usual Dosage	Millicoulombs of charge ¹⁷	<1-20 Hertz	Current >1 milliamperes (mA), Frequency 1-145 hertz	Not applicable
Contra-indications	Increased risk of complications in patients with unstable cardiac disease, ischemia, arrhythmias, hemorrhage, or increased intracranial pressure ¹⁷	Presence of conductive, ferromagnetic, or other magnetic-sensitive metals in the head or within 30cm of the treatment coil. Presence of implants controlled by physiological signals. ²⁵ Patients with high risk of seizure.	Bilateral or left cervical vagotomy. Patients with implants should not receive short wave diathermy, microwave diathermy, or ultrasound diathermy.	Patients with cognitive disorders, cognitive impairment, or limited cognitive functioning

“insufficient information exists to determine that general controls are sufficient to provide reasonable assurance of its safety and effectiveness.” (21 CFR860.3) The FDA is reconsidering how it classifies ECT.²⁶

ECT involves passing an electric current through the brain to produce a convulsion. Electrodes are usually placed at the bifrontal, bilateral, or right unilateral position. It is not commonly used as a first-line therapy or in primary care practice. The exceptions are uses in an emergency in which the person's life is at risk because of refusing to eat or drink or being in a catatonic state or in cases of attempted suicide. The effectiveness of ECT may be related to the stimulus parameters used, including position of electrodes, dosage, and waveform of electricity.

ECT is covered by major insurance plans, Medicaid, and Medicare. Reimbursement is approximately \$275 per treatment,²⁷ independent of the costs of inpatient hospitalization, should it be required. ECT usually consists of two to three treatments per week for 3 to 4 weeks.

ECT shows greater improvement in patients with suicidal intent than other antidepressant treatments; thus, it may be used as an early therapeutic option in suicidal patients.²⁸ Research also indicates that despite physical illness, coexisting diseases, or cognitive impairment, older patients tolerate ECT as well as younger patients and may demonstrate better response.^{29,30} Because ECT is a procedure that involves anesthesia, it also poses slight risks to patients from the procedure itself. Other potential risks include seizure and adverse cognitive effects.¹⁷

Repetitive Transcranial Magnetic Stimulation (rTMS)

rTMS involves magnetic focal stimulation through the scalp. The current elicited by the electromagnetic coil stimulates nerve cells in the region of the brain involved in mood regulation and depression. It can be administered in an office setting without the use of anesthesia. Patients may perceive it as less threatening than ECT.³¹ Patients having conductive, ferromagnetic, or other magnetic-sensitive metals in the head or within 30cm of the treatment coil should not undergo this procedure.²⁵ Sessions are usually 40 minutes in length, administered daily (usually only weekdays) for 2 to 6 weeks. rTMS costs between \$100 and \$300 per session.^{31,32} Medicare does not cover rTMS, although some private insurance plans cover it under limited circumstances.

rTMS is usually considered a reasonable option for acute treatment of TRD as opposed to VNS and pharmacotherapy, which are predominantly used as long-term treatments for TRD.³³ The FDA first approved this device in October 2008. The FDA states that rTMS is “indicated for the treatment of Major Depressive Disorder in adult patients who have failed to achieve satisfactory improvement from one prior antidepressant medication at or above the minimal effective dose and duration in the current episode.”³⁴ Possible side effects with rTMS include mild headaches, syncope, and transient hearing changes.²³ Although rTMS does pose a risk of seizure,³⁵ it reportedly does not have the cognitive risks of ECT.²³

Vagus Nerve Stimulation (VNS)

VNS involves surgically placed electrodes around the left vagus nerve. The VNS device consists of a round battery-powered generator that is implanted into the chest wall and attached to wires threaded along the vagus nerve. The therapy includes minor surgery, lasting approximately 30 to 60 minutes. Once implanted, the generator pulses the nerve for 30 seconds once every 5 minutes.³⁶ The total duration of this intervention is generally 10 weeks, although the stimulation can be extended for longer intervals.²⁴

VNS was first used in patients with epilepsy; it was also found simultaneously to improve mood.³⁷ The FDA approved VNS for TRD in July 2005, with labeled indication for “adjunctive long-term treatment of chronic or recurrent depression for patients 18 years of age or older who are experiencing a major depressive episode and have not had an adequate response to four or more adequate antidepressant treatments.”³⁸ The Centers for Medicare and Medicaid Services decided not to cover VNS in February 2007, citing lack of evidence.³⁶ VNS devices cost approximately \$10,000 to \$20,000, not including the cost of surgery and hospital fees. Although the initial cost of VNS is very high, it may save money for TRD patients in the long run. One study reported long-term savings with VNS compared with usual TRD care, estimating savings of \$2,974 and \$23,539 per patient per year at 5 and 8 years of device life, respectively.³⁹

The place in therapy for VNS may be for patients who have four or more adequate antidepressant treatment failures.⁴⁰ Considerations also include a longer onset of antidepressant action than other treatments, as VNS benefits for TRD may not be fully realized for 6 to 12 months.⁴¹ Further, VNS poses surgical risks and is associated with several side effects such as voice alteration, cough, neck pain, paresthesia, and dyspnea.⁴²

Cognitive Behavioral Therapy (CBT) or Interpersonal Psychotherapy (IPT)

Use of CBT began in the 1960s. It is a type of psychotherapy that aims to modify distorted, maladaptive, and depressogenic cognitions and related behavioral dysfunction.¹⁹ The therapist first introduces the patient to the cognitive model. Agendas, feedback, and psychoeducational procedures are used to structure sessions. To treat depressed patients with CBT, therapists emphasize negatively distorted thinking and deficits in learning and memory functioning.

Developed in the 1970s, IPT helps patients explore social and interpersonal issues that relate to depressive symptoms. Depressive symptoms identified are related to one of the four key problem areas: grief, disputes, transitions, and deficits.²⁰ After selecting a focus area, later sessions help the patient develop strategies to deal with the problem.⁴³

Both CBT and IPT have been studied extensively for depression, eating disorders, anxiety, and personality disorders, but understanding of their role in the treatment of TRD is more limited. Both therapies involve weekly sessions with the therapist, which last for 30 to 60 minutes. CBT may be carried out in a group setting if deemed beneficial for the patient. The therapy generally lasts from 3 to 4 months for acute phase treatment, although treatment duration may be for longer periods. Costs of CBT and IPT depend on the facility and the therapist; on average, these interventions cost around \$150 per session. Medicare currently covers CBT and IPT. FDA approval is not required for CBT or IPT since they do not include drugs or devices.

CBT and IPT do not have any risks or side effects associated with them. Patients need to have normal cognitive functioning to comprehend the therapist's questions. CBT and IPT are comparable psychotherapies for major depression and appear to be as effective as antidepressant medication treatment,⁴⁴⁻⁴⁶ although CBT may be more effective in patients with severe depression.⁴³

Pharmacologic Interventions

For many patients with TRD, the consideration of another pharmacologic intervention (whether a single agent or combination) remains the next decision step. To place the comparative effectiveness of nonpharmacologic treatments within the context of pharmacologic considerations, we also consider clinical outcomes for a next step pharmacologic treatment based on augmentation and combination medications commonly used in clinical practice.⁴⁷ Given the limited evidence base addressing this topic for TRD, we only consider pharmacologic information for clinical outcomes during acute phase treatment for our main population of interest (see Key Question [KQ] 1b below).

Patient Populations Included

Treatment resistance defined by prior treatment failures. The primary focus of this review is on patients with MDD who have had two or more failed prior treatment attempts within the current episode. Definitions of TRD vary considerably and controversially, most often by the

number of treatment failures (e.g., one failure, or one or more failures, or two or more failures), whether the treatment failures occur during the current episode, and whether treatment failures required different classes of antidepressants; no universally accepted definition of TRD currently exists.^{7,48-51} This variability is reflected in the differing operational definitions and selection criteria used for TRD trials. Nevertheless, a consensus appears to be forming around a definition of two or more treatment failures in the current episode.^{9,48} We view the most applicable evidence to be derived from *patients with two or more failures of treatment attempts that are of adequate dose and duration during the current depressive episode*. This population represents a group with known treatment resistance, and we believe these studies are most relevant to our KQs concerning efficacy, effectiveness, safety, and tolerability. However, given the evolving nature of the TRD definition, studies have often not clarified the number of failures within the current episode. Consequently, for the purposes of this report, we will define TRD as ***an episode of MDD that has not recovered following two or more adequate antidepressant medication treatments, regardless of the class of antidepressant used or whether the treatment failures were required to be in the current episode***.

The variance of the TRD classification makes interpretation of the available data involving our interventions of interest challenging. Studies addressing TRD and these nonpharmacologic interventions are not always designed with the above specifications in mind. Rather, some studies focus more broadly on the efficacy and/or safety of the interventions in populations of patients with poorly specified characteristics with respect to treatment failures. In particular, they may require patients to have only one previous treatment failure rather than two, or they may be conducted in samples of patients for whom the investigators have not been completely clear about failures but still give enough information to regard the subjects as “probable” failures (e.g., patients referred for ECT). In such studies, baseline characteristics may provide data indicating that a subset of these patients have two or more treatment failures; however, it is often unclear what proportion of the sample would fit the TRD definition of two or more failures selected for this report. Although these study populations do not involve homogenous TRD populations, their samples likely include a substantial proportion of TRD patients, and hence can provide data relevant to TRD. Consequently, although we will focus on studies strictly meeting our TRD definition, we will secondarily consider how data from two other groups of studies—those requiring one or more treatment failures (which involve patients with only one treatment failure as well as those with TRD) and those with probable TRD—may enhance our results.

Treatment-resistant depression defined for two classes of mood disorder. Studies of treatment resistance often consider patients with bipolar disorder in addition to patients with MDD. Our primary focus is evidence about TRD in study patients who clearly have MDD and not any other mood disorder. However, clinical trials of TRD patients frequently allow a mixture of MDD and bipolar disorder in their samples. Given that depressive episodes in MDD may have a different prognosis than those in bipolar disorder,⁵² such a mixture may distort the true effect seen in MDD-only patients. At the same time, studies in which a small fraction of the patient population has bipolar disorder rather than purely MDD are still likely to produce some information on the main topic (i.e., MDD alone). We attempted to select a threshold that would allow inclusion of studies with a proportion of bipolar disease that would not change the likelihood of response. No evidence exists that indicates a proper threshold for such a mixture. After conferring with a Technical Expert Panel, we chose to include trials in our synthesis when the patient population as a whole consists of no more than 20 percent bipolar patients, assuming that such a mix would not substantially alter outcomes from what one would see with MDD

alone. The type of bipolar diagnosis could include Type 1 (with manic episodes) or Type 2 (with hypomanic episodes).

Scope and Key Questions (KQs)

This review compares the efficacy, effectiveness, and harms of nonpharmacologic interventions for TRD in adults. To that end, we address the following six KQs. “Trials” in these KQs refers to treatment attempts, not experimental studies.

- KQ 1a. For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic¹ intervention), do nonpharmacologic interventions such as electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), or demonstrated effective psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute-phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- KQ 1b. How do these nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms after two or more failed adequate trials?
- KQ 2. For adults with TRD, do nonpharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence), whether as a single treatment or part of a combination treatment?
- KQ 3. Do nonpharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic [frozen or hyper] or psychotic symptoms)?
- KQ 4. For adults with TRD, do nonpharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to amnesia, memory loss, headaches, and postoperative complications.
- KQ 5. How do the efficacy, effectiveness, or harms of treatment with nonpharmacologic treatments for TRD differ for the following subpopulations:
 - Elderly or very elderly patients; other demographic groups (defined by age, ethnic or racial groups, and sex)?
 - Patients with medical comorbidities (e.g., seizure history, stroke, diabetes, dementia, perinatal depression, ischemic heart disease, cancer)?
- KQ 6. For adults with TRD, do nonpharmacologic interventions differ in regard to other health-related outcomes (e.g., quality of life)?

Organization of the Report

The remainder of this report describes our methods, presents the results of our synthesis of the literature, discusses our conclusions, and provides other information relevant to the interpretation of this work. The Methods chapter describes our scientific approach for this comparative effectiveness review in detail. The Results chapter presents our findings for all the KQs and subquestions; it includes summary tables as well. In the Discussion chapter, we summarize the findings, present the strength of evidence for critical comparisons or outcomes, and discuss the implications for practice and further research. A complete list of references is located immediately following the discussion chapter.

This report also contains the following appendices. Appendix A contains the exact search strings we used in our literature searches. Appendix B documents all the data abstraction forms and our quality rating criteria. Our excluded studies with reasons for exclusion are presented in Appendix C. Evidence tables appear in Appendix D. Appendix E is our table of scales used for measuring neurocognitive and other adverse effects. Appendix F lists our poor-quality studies and reasons for exclusion from relevant KQ analyses. Appendix G lists all sources from which we identified all of the studies for this review. Finally, Appendix H provides a listing of studies recommended for inclusion by peer and public reviewers of the prior draft version of the report. It is added here to help current readers of this report understand why well-known studies did not meet the inclusion criteria for this comparative effectiveness review.

Methods

In this chapter, we document the procedures that the Evidence-based Practice Center (EPC) used to develop this comparative effectiveness review (CER) on nonpharmacologic treatments for adults with treatment-resistant depression (TRD). We briefly describe the topic development process below. We then document our literature search and retrieval process and describe methods of abstracting relevant information from the eligible articles to generate evidence tables. We also document our criteria for rating the quality of individual studies and for grading the strength of the evidence as a whole.

Topic Development

The topic of this CER and preliminary questions arose through an open process involving the public, the Scientific Resource Center (SRC) for the Effective Health Care Program of the Agency for Healthcare Research and Quality (AHRQ) at Oregon Health and Science University, and various stakeholder groups. Our EPC was asked to develop provisional Key Questions (KQs) based on the issues submitted by the nominator of the topic. We conducted a preliminary literature review and worked with key informants to develop a set of provisional KQs. These KQs were posted by AHRQ for public comment before they were assigned to the RTI International-University of North Carolina EPC for this full CER.

Technical Expert Panel

In designing the study questions and methodology at the topic development stage, we consulted several technical and content experts, seeking broad expertise and perspectives. We worked with seven key informants and all were invited to participate in the Technical Expert Panel (TEP) for the full CER. Five accepted, and in one case a replacement from the consumer organization was made because the original person was no longer with the organization. In addition, we invited an expert in psychotherapy and another psychiatrist conducting a similar evidence review on pharmacotherapy options after one failed treatment, creating a total of eight members (listed in the Acknowledgements). We note that two TEP members had undisclosed conflicts of interest (COIs) related to the repetitive transcranial magnetic stimulation (rTMS) device that were identified during the course of the project. Upon further inquiry and clarification of the specifics of the form, both individuals filed amended COI forms.

To ensure robust, scientifically relevant work, we called on the TEP to provide reactions to work in progress and advice on substantive issues or possibly overlooked areas of research. Specifically, TEP members participated in conference calls and discussions through e-mail to:

- Review the KQs and analytic framework at the beginning of the project;
- Discuss the preliminary assessment of the literature, including inclusion/exclusion criteria and the review of the protocol; and
- Provide input on the information and categories included in evidence tables.

Our KQs were posted on AHRQ's Effective Health Care Web site on December 9, 2009. After discussions with the TEP, we added an additional question, KQ 1b, as described in the Introduction chapter.

Literature Search

Databases and Search Terms

To identify articles relevant to each of the six KQs defined in the Introduction chapter, we searched MEDLINE, Embase, the Cochrane Library, PsycINFO, and the International Pharmaceutical Abstracts. The full search strategy is presented in Appendix A. We used Medical Subject Headings (MeSH or MH) as search terms when available as well as key words when appropriate. The first step was to locate all articles on depression in human adults published in English. We combined terms for treatment-resistant depression, including the terms refractory, resistant, and drug resistance. The search was further narrowed to specific pharmacological and nonpharmacological treatments. Nonpharmacological interventions included socioenvironmental therapy, interpersonal psychotherapy (IPT), psychotherapy, cognitive therapy, cognitive behavioral therapy (CBT), electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), and vagus nerve stimulation (VNS). We searched for systematic reviews, clinical controlled trials, and nonexperimental studies in which the investigator did not assign group allocation. Sources were searched from 1980 to November 18, 2010.

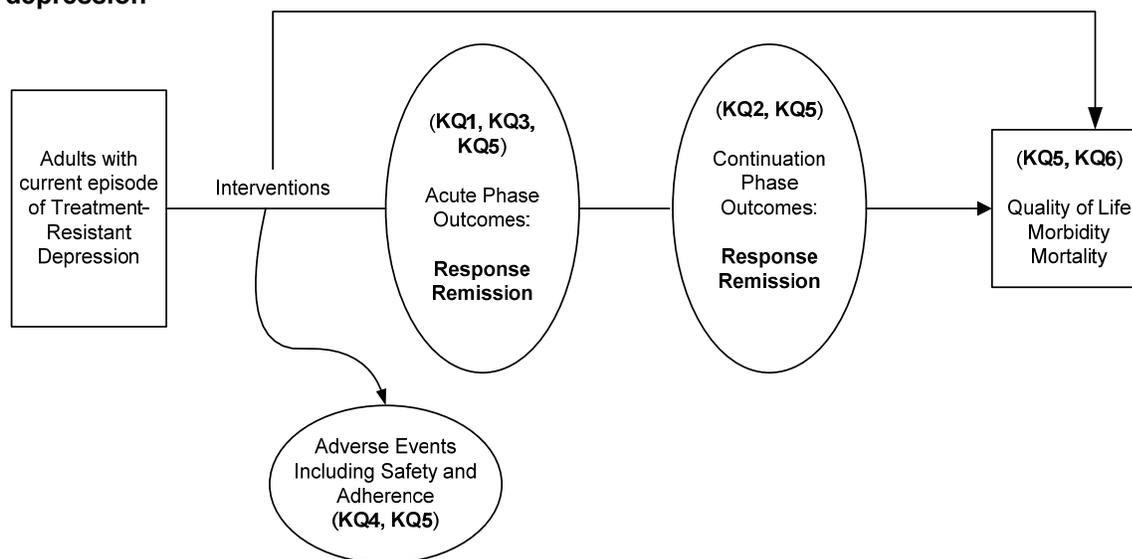
We used the National Library of Medicine publication type tags to identify reviews, randomized controlled trials (RCTs), and meta-analyses. We also manually searched reference lists of pertinent review articles and letters to the editor. We imported all citations into an electronic database (EndNote X3). Additionally, we hand-searched the Center for Drug Evaluation and Research database to identify unpublished research submitted to the U.S. Food and Drug Administration.

AHRQ SRC staff contacted device manufacturers and invited them to submit dossiers, including citations. We reviewed dossiers received from Cyberonics and Neuronetics. The SRC also provided our EPC with the results of their gray literature search: relevant articles, conference proceedings, and meeting abstracts to assist our center to identify other eligible studies that may not have been captured in the literature search.

Analytic Framework

Based on the six KQs, we developed an analytic framework to guide the systematic review (Figure 3). Specifically, the first two KQs pertain to the efficacy and effectiveness of obtaining (KQ 1) and maintaining (KQ 2) response and remission using these nonpharmacologic treatments; KQ 1 addresses the acute phase of treatment and KQ 2 the continuation or maintenance phases of treatment (as depicted in Figure 3). KQ 3 addresses response and remission for psychiatric subtypes of TRD (e.g., coexisting anxiety) and KQ 5 focuses on certain population subgroups (e.g., the elderly). KQ 4 focuses on safety and tolerability issues—that is, harms—with each of the interventions. Finally, KQ 6 looks at how these interventions affect other health outcomes, such as quality of life.

Figure 3. Analytic framework for nonpharmacologic interventions for treatment-resistant depression



Study Selection

To summarize, interventions included for one or more of the key questions (KQs) are:

- Nonpharmacologic therapies, for KQs 1–6:
 - ECT
 - rTMS
 - VNS
 - Evidence-based psychotherapy, specifically cognitive therapy (CBT or IPT)
- Pharmacologic,⁴⁷ for KQ 1b only, at least one of the antidepressants listed below:
 - Selective serotonin reuptake inhibitors (SSRIs): citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline
 - Serotonin-norepinephrine reuptake inhibitors: desvenlafaxine, duloxetine, mirtazapine, venlafaxine
 - Serotonin modulators: nefazodone and trazodone
 - Tetracyclic: mirtazapine
 - Other antidepressants: bupropion
 - Tricyclic antidepressants: amitriptyline, clomipramine, desipramine, doxepin, imipramine, maprotiline, mianserin, nortriptyline
 - Monoamine oxidase inhibitors (MAOIs): phenelzine, tranylcypromine
 - Augmentation strategies with methylphenidate; T4/cytomel; liothyronine; buspirone; lithium or amilsupride; aripiprazole; olanzapine; quetiapine; risperidone; ziprasidone.

For each KQ, we specified inclusion and exclusion criteria for studies and specified the outcome measures of interest (Table 2). For efficacy and effectiveness (all KQs except KQ 4), we first focused on head-to-head RCTs comparing one intervention with another. This body of work provides direct evidence about the comparisons. When sufficient head-to-head evidence was unavailable, we evaluated placebo- or sham-controlled evidence; in some cases, studies might have used “treatment as usual” as the control arm. In any of these cases, the evidence provides only indirect evidence. Systematic evidence reviews or meta-analyses based on a

systematic literature search were eligible for inclusion for each KQ. For reviewing adverse events (KQ 4), per our standard approach, we include observational studies. Finally, given the dearth of randomized controlled data that our preliminary review suggested was available for KQ 3 on psychiatric subtypes, KQ 5 on subgroups, and KQ 6 on quality of life, for these KQs we included observational studies (limited to prospective and retrospective cohort studies and case control studies). We do not formally distinguish efficacy from effectiveness trials.

Table 2. Key questions, outcomes, and study eligibility by key question

Key Question and Outcomes	Study Eligibility Criteria (Inclusion and Exclusion Criteria)
<p>KQ 1a and 1b Efficacy and effectiveness Outcomes</p> <ul style="list-style-type: none"> • Response • Remission <p>Measurement Scales</p> <ul style="list-style-type: none"> • Hamilton Rating Scale for Depression Scale (HAM-D) • Montgomery-Åsberg Depression Rating Scale (MADRS) • Beck Depression Inventory (BDI) • Inventory of Depressive Symptomatology • Clinical Global Impression (CGI) • Other relevant scales if none of the above is reported (e.g., Patient Health Questionnaire [PHQ-9]) 	<p>Study design KQ 1a:</p> <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. pharmacologic (an antidepressant, with or without additional pharmacologic agent[s]) • Good- or fair-quality meta-analyses or systematic evidence reviews <p>KQ 1b:</p> <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. placebo or sham • RCTs of pharmacologic (an antidepressant, with or without additional pharmacologic agent[s]) vs. placebo or sham • Good- or fair-quality meta-analyses <p>Minimum study duration</p> <ul style="list-style-type: none"> • Any duration <p>Sample size</p> <ul style="list-style-type: none"> • No minimum
<p>KQ 2 Maintenance of response or remission (or prevention of relapse or recurrence) Outcomes</p> <ul style="list-style-type: none"> • Relapse (continuation phase) • Recurrence (maintenance phase) <p>Measurement Scales</p> <ul style="list-style-type: none"> • All efficacy/effectiveness scales (see KQ 1 above) 	<p>Study design</p> <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • RCT designs include continued treatment for prevention or assessment of duration of effect after treatment stopped • Good- or fair-quality meta-analyses or systematic evidence reviews <p>Minimum study duration</p> <ul style="list-style-type: none"> • ≥ 1 month for relapse prevention • ≥ 3 months for recurrence prevention <p>Sample size</p> <ul style="list-style-type: none"> • No minimum
<p>KQ 3 Efficacy and effectiveness by subtype Outcomes</p> <ul style="list-style-type: none"> • Response • Remission <p>Measurement Scales</p> <ul style="list-style-type: none"> • All efficacy/effectiveness scales (see KQ 1 above) <p>Symptom Subtypes</p> <ul style="list-style-type: none"> • Psychotic-paranoia/hallucinations • Melancholic • Atypical • Postpartum 	<p>Study design</p> <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses or systematic evidence reviews • Observational studies (limited to prospective and retrospective cohort studies, case control studies) <p>Minimum study duration</p> <ul style="list-style-type: none"> • Any duration <p>Sample size</p> <ul style="list-style-type: none"> • No minimum

Table 2. Key questions, outcomes, and study eligibility by key question (continued)

Key Question and Outcomes	Study Eligibility Criteria (Inclusion and Exclusion Criteria)
<p>KQ 4 Safety, adverse events, and adherence Outcomes <ul style="list-style-type: none"> • Neurocognitive <ul style="list-style-type: none"> ◦ Amnesia ◦ Memory loss • Headaches • Postoperative complications • Other reported events • Discontinuations • Adherence/compliance Measurement Scales <ul style="list-style-type: none"> • All reported adverse events measurement scales • Discontinuations (overall and attributed to adverse events) • Adherence or compliance measures </p>	<p>Study design <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) Minimum study duration <ul style="list-style-type: none"> • Any duration Sample size <ul style="list-style-type: none"> • No minimum, case reports excluded </p>
<p>KQ 5 Population subgroups Outcomes <ul style="list-style-type: none"> • Response/remission • Relapse/recurrence • Adverse events • Discontinuations Measurement Scales <ul style="list-style-type: none"> • All efficacy/effectiveness scales (see KQ 1 above) • All reported adverse events measurement scales (see KQ 4 above) • Discontinuations and adherence rates Population Subgroups <ul style="list-style-type: none"> • Age • Medical comorbidity • Race or ethnicity </p>	<p>Study design <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) Minimum study duration <ul style="list-style-type: none"> • Any duration Sample size <ul style="list-style-type: none"> • No minimum, case reports excluded </p>
<p>KQ 6 Health-related outcomes Outcomes <ul style="list-style-type: none"> • Quality of life • Satisfaction/enjoyment • Physical or mental functioning • Work productivity or employment Measurement Scales <ul style="list-style-type: none"> • Global Assessment of Functioning Ability (GAF) • Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) • Medical Outcomes Study Short Form (SF-36, SF-12 or others) • Employment/productivity scales • Activities of daily living • Other relevant measures </p>	<p>Study design <ul style="list-style-type: none"> • RCTs of nonpharmacologic vs. nonpharmacologic • RCTs of nonpharmacologic vs. placebo or sham • Good- or fair-quality meta-analyses • Observational studies (limited to prospective and retrospective cohort studies, case control studies) Minimum study duration <ul style="list-style-type: none"> • Any duration Sample size <ul style="list-style-type: none"> • No minimum </p>

KQ = key question; RCT = randomized controlled trial

Two people independently reviewed article abstracts using the criteria presented in Appendix B for Level One. If both reviewers agreed that the study did not meet eligibility criteria, we excluded it; otherwise it moved forward to the next step for full-text review, Level Two. We retrieved the full articles for all studies retained at this stage.

Two reviewers then independently reviewed the full-text articles and applied a more detailed set of inclusion criteria; these involved explicit reasons for exclusion, such as wrong intervention, and wrong or no comparison group. Appendix B includes copies of all reviewer forms. We resolved conflicts about inclusion at this stage through consensus, with conflicts adjudicated by a third party. Studies excluded at this stage, along with reasons for exclusion, are listed in Appendix C.

For this review, results from well-conducted, valid head-to-head trials—that is, direct comparisons—provide the strongest evidence to compare treatments with respect to efficacy and harms. The many possible comparisons, set out in the Introduction chapter, are complex; in some cases, studies compared a treatment with a combination of that treatment and a second intervention. We defined head-to-head trials as those comparing one treatment with another treatment either by itself or in combination with other interventions.

We did not examine placebo-controlled or sham-controlled trials in detail if a sufficient number of head-to-head trials were available. If the published head-to-head evidence was limited, we reviewed placebo-controlled trials to provide an overview of efficacy. For harms (i.e., evidence pertaining to tolerability and adverse events), we examined data from both experimental and observational studies.

We did not set any minimum criteria for study duration or sample size, though case reports were excluded when observational study designs were allowed. The exception to this involved relapse and recurrence prevention studies, for which we required at least 1 and 3 months of followup, respectively.

We reviewed studies with health outcomes as primary outcome measures. Outcomes for efficacy or effectiveness, for example, were a decrease in depressive severity, treatment response and remission, quality of life, relapse, functional capacity, and hospitalization. We reviewed response and remission when based on changes in scores on depression scales as proxies for health outcomes (e.g., 50 percent improvement of depression scores for response). For harms, we looked for both overall and specific outcomes related to neurocognitive functioning, specific adverse events (e.g., amnesia, memory loss, headache), and procedure-related complications, recorded systematically and spontaneously, as well as tolerability as reflected by withdrawals and withdrawals attributable to adverse events.

Data Extraction and Analytic Strategy

We designed and used a structured data abstraction form to ensure consistency of data abstraction and quality appraisal for each study (reproduced in Appendix B). All data abstraction originally employed SRS 4.0 Mobius Analytics (available at: www.mobiusanalytics.com/e/index.cfm). Trained reviewers abstracted data from each included study into predesigned evidence tables for each KQ; they also assigned an initial quality rating (described below). A senior reviewer read each abstracted article, evaluated the accuracy and completeness of the data abstraction, and independently did a second quality rating. Final evidence tables can be found in Appendix D.

We abstracted data on study design, baseline population characteristics, specifications of the intervention, and relevant outcome assessments for both efficacy and harms. We abstracted data for the efficacy and quality-of-life outcome assessments when the studies used validated measures. We also abstracted data on compliance, attrition, and harms. Finally, we recorded whether analyses were done according to intention-to-treat methods if such information was

available in the articles. A detailed list of the data elements abstracted is presented in Appendix B.

Treatment Resistant Depression Definition and Tier Classification

As already noted, the definitions of TRD vary along several dimensions: How many previous treatment failures are considered? What types of treatments failed? Were dose and duration of previous treatments adequate? Were the failures during the current episode or over a lifetime? Moreover, the populations included in clinical studies differ by numerous factors. In regard to the variability of the definitions used in studies of TRD, as laid out in the Introduction chapter, we extracted specific information to create the three-tiered classification system used in presenting results in the Results chapter. We specifically collected data on the study's definition of a failed "trial" (i.e., a treatment in this context). These variables included a specific drug or drug class failed, the specified duration and/or dose of an "adequate" trial, the number of failed trials (whether in the current episode or in a previous, "lifetime," episode) required for inclusion, and baseline characteristics (i.e., the mean number of failed trials and other pertinent descriptors) of the sample.

Although our working definition of TRD is two or more treatment failures, we realize that many studies involving TRD populations often do not use this definition when formulating their inclusion criteria and that these criteria may not accurately reflect the average number of failed antidepressant trials for a study population. For example, although some studies may require only a single antidepressant failure for a participant to be included in a study, the inclusion criteria may not accurately indicate the average number of antidepressant failures for the study population, which could be higher than the cut point set by study inclusion criteria.

When devising the analytic strategy for this report, variation in study inclusion criteria and the overlap in the actual number of antidepressant failures were considered. As a function of our preliminary literature review, we realized that evolving definitions of TRD might prevent inclusion of studies with data relevant to our population of interest. For example, studies conducted at a time when resistance was understood to be one or more treatment failures might have nearly a complete population of patients with TRD (two or more treatment failures), but because the analyses did not allow results to be stratified by having two or more treatment failures, such a study would be excluded. Also, studies in which the number of prior treatment failures was not specified but where the likelihood of TRD was high, such as with many ECT trials, would also be excluded. We believed that not including such studies would not accurately reflect the available evidence base for TRD.

Accordingly, we considered options and discussed possible approaches with our TEP, who supported the use of a tiered study classification system. We have attempted to maintain our focus on study populations meeting our TRD definition (≥ 2 antidepressant failures) while not excluding potentially relevant evidence.

Our approach to stratifying the literature—into three "tiers"—is highlighted in Table 3. We primarily differentiate studies based on how investigators for the included studies defined TRD:

Table 3. Relevance to TRD per CER protocol by Tiers of evidence pertaining to populations involving varying proportions of treatment-resistant depression

Population	Tier 1. TRD per CER Protocol (All Patients Required to Have ≥ 2 Treatment Failures)	Tier 2. All Patients Required to Have ≥ 1 Prior Treatment Failures	Tier 3. Involves Those With Probable TRD (But Number of Treatment Failures not Specified)
MDD alone	All MDD patients who failed ≥ 2 previous treatments	All MDD patients who failed ≥ 1 previous treatment	All MDD patients with TRD not defined
Mixed MDD and bipolar disease, with bipolar patients constituting $> 0\%$ but $\leq 20\%$ of the study population	MDD/bipolar mix who failed ≥ 2 previous treatments	MDD/bipolar mix who failed ≥ 1 previous treatment	MDD/bipolar mix with TRD not defined

CER = comparative effectiveness review; MDD = major depressive disorder; TRD = treatment-resistant depression

- **Tier 1** evidence: involves studies requiring failure to recover following two or more adequate antidepressant treatment trials (Tier 1, our working definition of TRD).
- **Tier 2** evidence: involves studies requiring patients to have one or more failed adequate antidepressant treatment trials; may include both those with only one prior treatment failure in addition to those with two or more failed trials. By virtue of including those with only one failure, on average this group has an overall lesser degree of treatment resistance than TRD patients (Tier 1).
- **Tier 3** evidence: involves studies where the number of prior failed treatments was not specified but the clinical situation suggested a high probability of patients having two or more failed prior antidepressant trials; these data have probable relevance to TRD. For example, an included study may refer to TRD without characterizing it, or the clinical presentation may strongly suggest two or more prior treatment failures. Studies that did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

Psychiatric Diagnosis

Also, as described in the Introduction chapter, we included study populations of patients with major depressive disorder (MDD) and study populations that include a small number of patients with bipolar disorder. We explicitly extracted data regarding the psychiatric diagnosis—that is, MDD or bipolar disorder—to allow us to limit the percentage of patients with a bipolar TRD to ≤ 20 percent, a proportion that we determined would be unlikely to influence the outcomes from what was expected for an MDD TRD population. If the study clarified whether the included bipolar patients were Type 1 (with manic episodes) or Type 2 (with hypomanic episodes), we collected this information.

Nonpharmacologic Intervention Treatment Characteristics

During data abstraction, characteristics of each mode of nonpharmacological intervention that affected treatment dose or intensity were collected and used in our analytic approach. Parameter variables were unique for each mode of intervention. For ECT, data were collected on the location of the stimuli (e.g., unilateral/bilateral), treatment intensity (e.g., as a function of seizure threshold), number of treatments per week, and mean number of treatment sessions. In the

Results chapter, ECT implementation for an intervention group is described using the proportion receiving bilateral stimulation and the mean number of treatment sessions received; additional treatment description parameters are listed in the evidence tables (Appendix D).

For rTMS, data were abstracted on the location of stimuli (e.g., left or right dorsolateral prefrontal cortex); frequency (e.g., hertz [Hz]) and intensity (e.g., as a function of motor threshold) of the stimuli; stimuli or pulses per session (abbreviated “pps”); total number of sessions; and duration of treatment (in weeks). These variables were not always presented in this fashion within our included studies. The following formula was used to calculate pps when the number of treatments per week was not explicitly provided: frequency (Hz) times the duration of each train (seconds) times the number of trains equals pps.²¹

A range of treatment parameters for both active and sham stimulations are used in rTMS efficacy studies. In the treatment of depression, stimuli are most often applied at either a high frequency (> 1 Hz) to the left or low frequency (\leq 1 Hz) to the right dorsolateral prefrontal cortex.²¹ To simplify reporting in the Results chapter, the location of stimulation and frequency is specified only in studies deviating from these conventions. All other interventions are described as either high rTMS or low rTMS and complete descriptions of all rTMS stimulation parameters as provided in individual studies are reported in the evidence tables (Appendix D).

Some methods of sham rTMS have been shown to have a smaller but noteworthy amount of active stimulation.^{53,54} If an included study used one of these methods of sham stimulation, investigators assessed the possibility that it affected the results of the study with potential issues acknowledged in the description of the results. Full descriptions of all sham stimulation parameters are found in the evidence tables (Appendix D).

For VNS, data were collected on the frequency (Hz), pulse width (in seconds), on/off cycle schedule, and duration of treatment. Only treatment parameters outside of the standard range are described in the results; full intervention methodologies, including sham stimulation procedures, are presented in the evidence tables (Appendix D).

Lastly, for psychotherapeutic interventions, data were collected on the method of therapy implementation (i.e., individual or group therapy), content of the curriculum (e.g., cognitive-based therapy), intensity of the treatment (in sessions per week), total number of sessions, and treatment duration (in weeks). Psychotherapeutic interventions are defined by curriculum content in the results; other parameters are reported in the evidence tables (Appendix D).

Antidepressant Medication Treatment Strategy

In addition to the nonpharmacologic interventions used in studies, investigators used different strategies for managing patients’ antidepressant pharmacotherapy that included antidepressants and augmenting agents such as antipsychotics and mood stabilizers. All included studies were categorized into one of five groups according to how the antidepressant pharmacotherapy is addressed as part of a study design. Antianxiety medications were allowed by some studies; however, these medications were not assessed as part of the antidepressant strategy categorization as there is no evidence basis supporting their benefit as an augmentation agent.

Switch studies are those in which all patients discontinued their prior antidepressant treatment before initiating their next step treatment. Other studies allowed patients to continue their prior antidepressant pharmacotherapy and initiated next step treatment as an add-on or augmentation to their current treatment; these treatment strategies were termed *augmentation* strategies. In some augmentation studies, a small proportion of patients were not taking any psychotropic

medications before or during the trial. The inclusion of such patients is acknowledged in the study description.

A third set of studies used both switch and augmentation strategies and were categorized as *mixed*. Two types of mixed studies exist in the included literature. One group of studies encourages but does not require patients to discontinue their antidepressant medications, resulting in a study population that contains both switchers and augmenters in all study groups. Studies that allow different antidepressant medication strategies within research groups are called *mixed-within*. Other studies compare patients who *switch* to patients who *augment*; these studies use a mixed antidepressant medication strategy with between-group differences and are called *mixed-between*.

In another subset of studies, all patients initiated a new psychotropic medication at the same time in which active groups began the nonpharmacologic intervention. This strategy was termed *combination treatment*. Lastly, in a small group of studies, medications were not limited or initiated by the study (e.g., patients sought treatment as usual, which allowed them to change medications or continue the same regimen at the discretion of their treating doctor). This group of studies was described as having an *unlimited* psychotropic medication strategy. A small number of studies allowed (or disallowed) antidepressant medications and potential augmenting agents differently (e.g., antidepressants were discontinued but patients were allowed to continue antipsychotics); pharmacologic strategies of these studies are described in the text and summary tables. Details of each study’s antidepressant medication strategy are provided in the evidence tables (Appendix D).

Disease Severity

Lastly, to enable us to examine differences based on disease severity, we grouped baseline scores into three categories: none to mild, moderate, and severe to very severe (Table 4).⁵⁵

Table 4. Categories of depressive severity

Instrument	None/Mild	Moderate	Severe/Very Severe
HAM-D ₁₇	≤ 13	14–19	≥ 20
HAM-D ₂₁	≤ 15	16–22	≥ 23
HAM-D ₂₄	≤ 18	19–26	≥ 27
MADRS	≤ 19	20–34	≥ 35
BDI	≤ 18	18–29	≥ 30
QID-SR	≤ 10	11–15	≥ 16

BDI = Beck Depression Inventory; HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Åsberg Depression Rating Scale; QID-SR = Quick Inventory of Depressive Symptomatology—Self-Report.

Quality Assessment

To assess the quality (internal validity or risk of bias) of all included studies, we used predefined criteria based on those described in the AHRQ Methods Guide for Comparative Effectiveness Reviews (ratings: good, fair, poor).⁵⁶ Two independent reviewers assigned quality ratings. They resolved any disagreements by discussion and consensus or by consulting with a third reviewer.

Elements of quality assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; overall and differential loss to followup; and the use of intention-to-treat analysis. We assessed observational studies based on the potential for selection bias (methods of selection of subjects and loss to followup), potential for measurement

bias (equality, validity, and reliability of ascertainment of outcomes), adjustment for potential confounders, and statistical analysis.

In general terms, a “good” study has the least bias, and results are considered to be valid. We rated studies that met all criteria as good quality. “Fair” studies presumably fulfilled all quality criteria but did not report their methods to an extent that answered all of our questions. A fair study is susceptible to some bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A “poor” rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting large amounts of missing information, or discrepancies in reporting) that may invalidate the study’s results. Studies that had a fatal flaw (defined as a methodological shortcoming that leads to a high probability of bias) in one or more categories were rated poor quality.

Poor-quality studies and reasons for that rating are presented in Appendix F. In this CER, we excluded poor-quality studies from our analyses if there were enough good or fair studies with significant findings. In some cases, a poor study may offer the only pertinent information about an important outcome or comparison, and we may comment on it in the relevant section of Results but it will not be included in summary tables there.

Applicability Assessment

Using the parameters for evaluation on guidance provided by AHRQ’s Methods Guide for Comparative Effectiveness Reviews,⁵⁷ we evaluated the applicability of the studies included and evaluated in this CER. Applicability is essentially the generalizability or external validity of the studies included in the evidence base. We evaluated applicability using a qualitative assessment of the population, intervention/treatment, comparator, outcomes measured, timing of followup, and setting. We specifically considered whether populations enrolled in these trials or studies differed from target populations as laid out above, whether studied interventions are comparable with those in routine use, whether comparators reflect best alternatives, whether measured outcomes reflect the most important clinical outcomes, whether followup was sufficient, and whether study settings were representative of most settings.

Grading Strength of a Body of Evidence

We evaluated the strength of evidence based on the AHRQ Methods Guide for Comparative Effectiveness Reviews.⁵⁶ Strength of evidence is graded only for major comparisons and major outcomes for the topic at hand. The strength of evidence for each outcome or comparison that we graded incorporates scores on four mandatory domains: risk of bias, consistency, directness, and precision; it can also reflect ratings for other domains that can be factored in when relevant (e.g., dose-response relationships). As described in Owens et al., the evaluation of risk of bias includes assessment of study design and aggregate quality of studies.⁵⁶ We judged good-quality studies with strong designs to result in evidence with low risk of bias. We graded evidence as consistent when effect sizes across studies were in the same direction and had a narrow range. When the evidence linked the interventions directly to health outcomes, we graded the evidence as being direct. For active versus sham control comparisons, we graded the evidence as direct for general efficacy, which should not be interpreted as direct comparative effectiveness for the head-to-head comparisons considered in this report (e.g., rTMS vs. VNS, rTMS vs. ECT). For the main head-to-head comparisons for this report (ECT, rTMS, VNS, and psychotherapy), we graded evidence as being precise when results had a low degree of uncertainty. We had two separate

reviewers evaluate the overall strength of evidence for each major outcome based on a qualitative assessment of strength of evidence for each domain and reconciled all disagreements. The levels of strength of evidence are shown in Table 5. We present our strength of evidence findings for TRD (Tier 1 studies) in our overview sections.

Table 5. Strength of evidence grades and their definitions

Grade	Definition
High	High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
Moderate	Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
Low	Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
Insufficient	Evidence either is unavailable or does not permit estimation of an effect.

Data Synthesis

Although we use the tiers as a guide to describe all the included evidence, our primary focus is on the populations with a Tier 1 TRD definition (two or more previous treatment failures). Some studies do not clarify whether failures occurred in a “current” episode or during one or more previous episode(s) (which can be characterized as over a “lifetime”). For that reason, our tiers may include a mix of studies that assess failing treatments in the current episode or failing treatments over a more extended period that may involve more than one episode. We highlight this distinction as appropriate. We also highlight other aspects of how treatment resistance, diagnosis, or severity of illness might vary.

For each KQ, we first present an overview of the particular comparison, including the strength of evidence findings for the Tier 1 studies. This section is followed by a key points section, which highlights important findings from the relevant comparisons, first for Tier 1 and then for Tiers 2 and 3. Finally, we present a detailed analysis section, which describes the individual studies, beginning with Tier 1 and followed by Tiers 2 and 3, in more detail. If possible, we report quantitative analyses as described below.

As described above, a complex and broad array of factors have the potential to shape the answers to the KQs. Throughout this report we synthesized the literature qualitatively.

If data were sufficient, we also augmented findings with quantitative analyses. We first quantitatively synthesized results for our primary focus, TRD (Tier 1) studies. Further, to assess how consideration of Tiers 2 and 3 affects Tier 1 findings alone, we also quantitatively synthesized results for Tiers 1, 2, and 3 combined to allow a comparison with Tier 1 alone.

We conducted meta-analyses of data for comparisons involving trials that were fairly homogenous in study populations, treatment intervention, and outcome assessments. For efficacy, we used three outcome measures:

1. The weighted mean difference of changes on the Hamilton Rating Scale for Depression (HAM-D). We chose this outcome measure to have an estimate of the actual difference in effect sizes between treatments.
2. The relative risk (RR) of being a responder (more than 50 percent improvement from baseline) on the HAM-D or the Montgomery-Åsberg Depression Rating Scale (MADRS) at study endpoint.

3. The RR of achieving remission on the HAM-D or MADRS at study endpoint. The HAM-D definition for the 17-item version was ≤ 8 , and for the 21-item version was ≤ 10 . For the MADRS, the remission definition was a score of ≤ 8 . If a study used a slightly different definition for remission, this difference was noted in the study's summary table and was included if, in the authors' judgment, it did not substantially differ from the above.

For each meta-analysis, we conducted a test of heterogeneity (I^2 index) and applied both a random and a fixed-effects model. We report the results from random effects models because, in all meta-analyses, the results from random and fixed effects models were very similar. If the RR was statistically significant, we calculated the number needed to treat (NNT) from the pooled RR or the pooled risk differences if variations in baseline risks were small.

We assessed publication bias using funnel plots and Kendall's tests. However, given the small number of component studies in our meta-analyses, these tests have low sensitivity to detect publication bias.

If meta-analyses were not possible but we deemed that an estimation of a treatment effect was of particular interest, we conducted descriptive statistics of the above-mentioned outcome measures. We calculated weighted means and 95 percent confidence intervals of changes on HAM-D or MADRS, and the percentages of responders and remitters for specific interventions or treatment strategies. The findings provide an estimate of the average, expected treatment effect for a specific intervention. Nevertheless, they have to be interpreted cautiously. Because of the lack of control groups, no general efficacy can be inferred from such results. Furthermore, the magnitude of treatment effects should not be compared across interventions.

Peer Review

This CER received external peer review from the TEP members and individuals who were experts in fields relevant to TRD (listed in the front matter) and from various stakeholder and user communities. The SRC managed the peer review process. If reviewers provided additional references to consider for inclusion in the final report, we reviewed all suggested references and included those that were appropriate and within the scope of this CER. We also addressed all comments and revised the report accordingly.

Results

Introduction

This chapter presents the results of our synthesis of the evidence on all six key questions (KQs, summarized in Table 6) about nonpharmacologic interventions for treating patients with treatment-resistant depression (TRD). To summarize, for all KQs except KQ 1, we are concerned with four major nonpharmacologic interventions: electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy or interpersonal psychotherapy (CBT or IPT). As noted in Table 6, KQ 1b asks about pharmacologic interventions in patients who have two or more previous treatment failures.

This chapter is organized as follows: first by KQ, second by intervention comparison, third by type of treatment failure (i.e., tier), and then by major depressive disorder (MDD) or MDD and bipolar study populations. In addition, according to the specifications from the Agency for Healthcare Research and Quality for comparative effectiveness reviews, within each KQ section, we present an overview, then key points, and finally detailed analyses. Finally, as explained in the Methods chapter, we graded the strength of evidence for all major comparisons and outcomes. We provide our readers with the strength of evidence findings for TRD (Tier 1 studies) in the Overview sections for each KQ.

We focus in this chapter chiefly on trials, which can be head-to-head investigations or trials with control arms involving sham procedures or, for behavioral interventions, various forms of “usual care” that can include physician (psychiatrist) visits, medications, or both. For KQ 4 on harms, we also include observational studies. Evidence tables for all studies are presented in Appendix E.

We include information only on studies for which our quality ratings were good or fair; most studies were rated fair, so we specifically call out quality ratings only for good trials or studies. Poor-quality studies are listed in Appendix G; in the very few cases in which a poor-quality study may have had the only relevant information on a major comparison or outcome, we will cite information about statistically significant findings in the detailed analysis text. Summary tables in the detailed analyses subsections have only good or fair quality studies.

We identified 2,444 citations from searches across databases. Additionally, we detected 310 articles from manually reviewing the reference lists of pertinent review articles. Figure 4 documents the disposition of the 79 articles in this review. Of the total 2,754 abstracts screened, 1,896 citations were excluded. Working from 858 articles retrieved for full review, 779 were excluded at this stage (Appendix D). Of the studies excluded at the full review, 269 were excluded for no or wrong comparison, 249 were excluded for including the wrong population, 137 were excluded for wrong publication type, 53 were excluded due to the analysis of outcomes

Table 6. Key questions about treatment-resistant depression (TRD)

Key Questions
KQ 1a. Efficacy of nonpharmacologic interventions for acute-phase TRD (response or remission)
KQ 1b. Efficacy of pharmacologic interventions for acute-phase TRD (response or remission), for patients with two or more prior treatment failures
KQ 2. Efficacy for maintaining response or remission (e.g., preventing relapse or recurrence)
KQ 3. Efficacy for acute-phase TRD as a function of particular symptom subtypes (e.g., catatonia or psychosis)
KQ 4. Harms of nonpharmacologic interventions (i.e., safety, adverse events, or adherence issues)
KQ 5. Efficacy or harms of nonpharmacologic treatments for selected subgroups defined by sociodemographic characteristics or coexisting conditions
KQ 6. Health-related outcomes of nonpharmacologic treatments (e.g., quality of life)

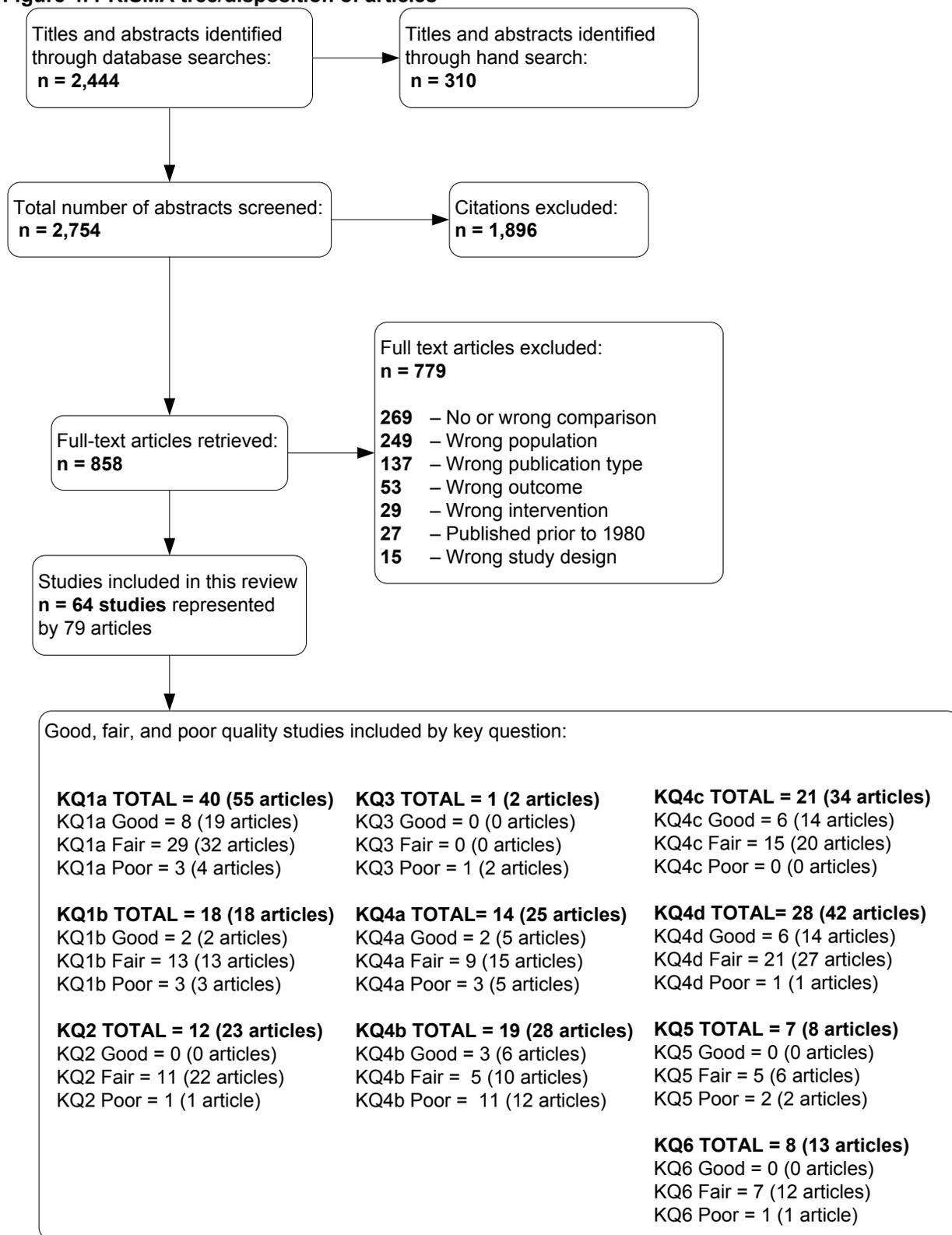
not of interest, 29 were excluded for performing analysis on an intervention not of interest, 27 were excluded for a publishing date prior to 1980, and 15 were excluded because the study was the wrong study design. We included 79 published articles reporting on 64 studies: 62 randomized controlled trials (RCTs) (77 articles) and 2 observational studies (2 articles). Evidence tables for included studies, by key question, can be found in Appendix E.

Of the 79 included articles, 17 (22 percent) were supported by pharmaceutical or device manufacturers; 48 (61 percent) were funded by governmental or independent funds. We could not determine the source of support for 14 (17 percent) studies.

Of the included studies, there were 17 head-to-head RCTs (19 articles): 7 studies (9 articles) were head-to-head RCTs of a non-pharmacologic intervention versus a nonpharmacologic intervention; 3 were head-to-head RCTs of a nonpharmacologic intervention versus a pharmacologic one; and 7 were head-to-head studies of a pharmacologic versus pharmacologic intervention. Further, there were 38 additional RCTs (50 articles) that were sham- or placebo-controlled, and 2 observational studies (2 articles). We excluded eight studies (eight articles) because of poor quality.

Most included studies were relevant for more than one KQ. For KQ 1a a total of 40 studies (55 articles) were included. Of these studies, 8 (19 articles) were rated as good and 29 (32 articles) were rated fair quality for internal validity. KQ 1b included 18 studies (18 articles), of which 2 studies (2 articles) were rated as having good internal validity and 13 studies (13 articles) were rated as having fair internal validity. For KQ 2, a total of 12 studies (23 articles) were included. Of these studies, none were rated as good. Eleven studies in KQ 2 (22 articles) were rated as fair quality for internal validity. No studies with good or fair internal validity were identified for KQ 3. For KQ 4a, a total of 14 studies (25 articles) were included. Of these studies, two studies (five articles) were rated as good. Nine studies in KQ 4a (15 articles) were rated as fair quality for internal validity. KQ 4b included 19 studies (28 articles), of which 3 studies (6 articles) were rated as having good internal validity and 5 studies (10 articles) were rated as having fair internal validity. For KQ 4c, a total of 21 studies (34 articles) were included. Of these studies, 6 studies (14 articles) were rated as good. Fifteen studies in KQ 4c (20 articles) were rated as fair quality for internal validity. KQ 4d included 28 studies overall (42 articles), of which 6 studies were good (14 articles) and 21 studies (27 articles) were rated as fair. KQ 5 included a total of seven studies (eight articles). No studies were rated as good, and five studies (six articles) were rated as fair. For KQ 6, a total of 8 studies (13 articles) were included, 7 of which were rated as having fair internal validity, while no studies were rated as having good internal validity.

Figure 4. PRISMA tree/disposition of articles



*Articles were included for more than one KQ

Reasons for exclusion were based on eligibility criteria or methodological criteria. Studies that originally met eligibility criteria but were later rated as poor quality for internal validity are located in Appendix E. Eight distinct studies were excluded from consideration for any of the KQs because of poor quality. Eleven studies were included in the review that were rated as fair or good quality and included certain key questions (e.g., KQ 1a), but were rated as poor for other key questions and hence excluded (e.g., KQ 4b). For KQ 1a, three studies (four articles) were rated as poor. KQ 2, KQ 3, and KQ 6 each rated one study as poor. KQ 1b excluded three studies for poor internal validity. Of the studies applicable to KQ 4a, three studies (five articles) were rated as having poor internal validity. KQ 4b excluded 11 studies (12 articles) for poor internal validity. For KQ 4c, no poor studies were identified. One study was rated as having poor internal validity in KD 4d. KQ 5 excluded two studies (two articles) for poor internal validity. The main reason for rating as poor of studies was due to poor reporting of methodology.

Key Question 1: Organization of Results

The presentation of KQ 1, which deals only with efficacy and effectiveness of interventions undertaken in acute phase treatment, is complex. Such clinical outcomes are one of a number of variables guiding the selection of therapy. Other considerations in acute phase treatment—such as effectiveness for subgroups, harms, and other health-related outcomes like quality of life—are addressed by KQs 3 through 6. KQ 2, in contrast, assesses the role of treatment selection in maintaining response or remission during continuation phase treatment.

Our primary focus is on comparisons of nonpharmacologic interventions—ECT, rTMS, VNS, and psychotherapy—presented as KQ 1a. We present evidence that stratifies first by which interventions are being compared, then by tier, and then by whether the population was MDD-only or MDD/bipolar mix. Within each tier, we attempt to assess the effect on outcomes of key PICOTS (patient population, intervention, comparison, outcome, and timeframe) elements: whether the population is MDD versus MDD/bipolar mix; whether treatment failure is required in the current episode; the level of depressive severity; treatment characteristics (e.g., number of treatment sessions, treatment location); and treatment strategy (e.g., whether patients switched to a new treatment or added a new treatment to augment their current treatment). We focus on Tier 1 TRD data first, and then we consider potentially relevant data from Tiers 2 and 3. We begin by reviewing this head-to-head literature.

Given the limited number of head-to-head comparisons available, we also review the nonpharmacologic interventions versus control to assess whether we might be able to extend our analyses through indirect comparison. Such indirect analyses require a suitable number of comparisons with placebo or sham groups across the interventions.

Next, in KQ 1b, we compare nonpharmacologic to pharmacologic interventions. We present the evidence in a similar order. First, we review head-to-head nonpharmacologic versus pharmacologic comparisons. Second, we review available pharmacologic versus pharmacologic literature addressing response to antidepressant management to provide a comparison of what might be expected with a next-step pharmacologic treatment for TRD. These comparisons involve only MDD-only, Tier 1 study populations. In reviewing the pharmacologic literature, we attempt to identify adequate control groups that would allow us to generate indirect measures of the relative outcomes of pharmacologic versus control interventions that we can compare to the nonpharmacologic effect sizes. Throughout KQ 1, we provide a qualitative synthesis of the evidence; this synthesis is paired with a quantitative analysis of this data when an adequate number of studies are identified.

Our main outcomes of interest are changes in depressive severity, rates of response, and rates of remission. Most studies report these outcomes using a version of the Hamilton Rating Scale for Depression (HAM-D), so we focus on this result; however, in the absence of HAM-D scores, we used Montgomery-Asberg Depression Rating Scale (MADRS), Beck Depression Inventory (BDI), or Quick Inventory of Depressive Symptomology (QIDS-SR) scores. In Table 7, information is provided for these scales. For each outcome, we report the results of appropriate statistical tests comparing results between groups. All statistics are based on an intention-to-treat analysis unless otherwise specified. In studies in which the mean change in depression severity or proportion of responders or remitters is not reported but in which sufficient information is provided to calculate these variables, we made the calculations and include this information in the tables. To assist the reader making comparisons between studies, the proportion of responders and remitters is shown as a function of the number of participants randomized (i.e., an intention-to-treat [ITT] analysis); statistical analyses calculated using a completers, per-protocol, or modified-ITT analysis are identified as such in the summary tables. We also categorized each population for depression severity using the chart described in Table 4 of the Methods section. We consider only studies assessed as good or fair quality.

Table 7. Abbreviations and full names of diagnostic scales and other instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range of Scores	Improvement Denoted by
BDI	Beck Depression Inventory	0-63	Decrease
HAM-D ₁₇	Hamilton Rating Scale for Depression – 17 item	0-52	Decrease
HAM-D ₂₁	Hamilton Rating Scale for Depression – 21 item	0-64	Decrease
HAM-D ₂₄	Hamilton Rating Scale for Depression – 24 item	0-75	Decrease
HAM-D ₂₅	Hamilton Rating Scale for Depression – 25 item	0-52	Decrease
MADRS	Montgomery-Asberg Depression Rating Scale	0-60	Decrease
QID-SR	Quick Inventory of Depressive Symptomology – Self Report	0-27	Decrease

Key Question 1a: Nonpharmacologic Interventions—Overview of Head-to-Head Comparisons

Six head-to-head comparisons were available, four comparing ECT with rTMS and two comparing ECT with a combination of ECT plus rTMS (Table 8).

Table 8. Number of good- and fair-quality studies by comparison, tier, and diagnostic mix for KQ 1a

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT versus rTMS	Tier 1 (≥ 2 treatment failures)	1	0
ECT versus rTMS	Tier 2 (≥ 1 treatment failures)	1 additional	0
ECT versus rTMS	Tier 3 (probable treatment failures)	0	2 additional
ECT versus ECT plus rTMS	Tier 1 (≥ 2 treatment failures)	1	0
ECT versus ECT plus rTMS	Tier 3 (probable treatment failures)	1 additional	0

ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation

Of the four studies (reported in six articles) that compared ECT with rTMS,⁵⁸⁻⁶³ only one was in a Tier 1 MDD population.⁵⁸ Both this study and the single Tier 2 MDD study⁵⁹ found no significant differences between groups. However, a good-quality Tier 3 MDD/bipolar mix study found a greater change in depressive symptomatology and higher response and remission rates in the ECT group.^{61,63} A second Tier 3 study rated fair supported these results showing higher response and remission rates in the ECT group.⁶⁰

Of the two studies comparing ECT with a combination of ECT and rTMS, both were in an MDD population; one was in a Tier 1 study⁶⁴ and the other was Tier 3.⁶⁵ These two studies showed no difference in outcome between treatments.

All studies included patients with severe depression, and none required a failure in the current episode, preventing an assessment of the role of these variables on outcome. For studies comparing ECT with rTMS, the two Tier 3 studies favored ECT while the Tier 1 and 2 studies showed no difference in outcomes, but the limited number of studies limit observation of any true pattern.

We could not assess how type of treatment strategy affected outcomes because of the limited number of studies and the multiple types of treatment strategies used. Studies varied by whether the trial tested interventions as a switch strategy (switching from the current failed treatment to a new strategy),^{58,59,65,66} or an augmentation strategy (adding the new intervention to the current regimen).⁶⁰⁻⁶³ Finally, some studies compared combinations of treatments (such as ECT versus ECT plus rTMS).^{64,65}

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. One study provides a low strength of evidence that there were no differences in depressive severity, response rates, or remission rates between switching to ECT versus switching to rTMS (Table 9).⁵⁸ Similarly, a second study provides a low strength of evidence that there were no differences in changes in depressive severity or between groups augmenting with ECT or with ECT plus rTMS (Table 10).⁶⁴ Results from both studies are limited by a small sample size.

Table 9. Strength of Evidence: Efficacy of ECT versus rTMS

Outcome	Number of Studies; Subjects	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low
Response	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low
Remission	1; 42	Medium RCT 1 fair	Unknown	Direct	Imprecise	No significant difference Low

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Table 10. Strength of Evidence: Efficacy of ECT plus rTMS versus ECT

Outcome	Number of Studies; Subjects	Risk of Bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 22	Medium RCT 1 fair	Unknown	Indirect (compares combination to ECT rather than rTMS to ECT)	Imprecise	No significant difference Low
Response	0; 0	—	—	—	—	—
Remission	1; 22	Medium RCT 1 fair	Unknown	Indirect (compares combination to ECT rather than rTMS to ECT)	Imprecise	No significant difference Low

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Key Question 1a: Nonpharmacologic Interventions—Key Points of Head-to-Head Comparisons

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Two fair MDD-only studies, one Tier 1⁵⁸ and one Tier 2,⁵⁹ found no differences in changes in depressive symptomatology, response, or remission. However, a good-quality Tier 3 MDD/bipolar mix study found a greater change in depressive symptomatology and higher response and remission rates in the ECT group;^{61,63} a second Tier 3 study rated fair supported these results, showing higher response and remission rates in the ECT group.⁶⁰

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Two fair studies, one Tier 1 MDD-only⁶⁴ and one Tier 3 MDD-only,⁶⁵ found no difference in changes in depressive symptomatology, response, or remission.

Key Question 1a: Nonpharmacologic Interventions—Detailed Analysis of Head-to-Head Comparisons

Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

One trial comparing ECT with rTMS was identified in Tier 1 (Table 11).

Table 11. Efficacy of ECT versus rTMS: Tiers 1–3

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
<p>Rosa et al., 2006⁵⁸ 2–4 weeks of active treatment (after week 2, rTMS non-responders withdrawn with LOCF) Tier 1: Did not require failure in the current episode Fair</p>	<p>ECT (n = 20) % bilateral NR, mean number of sessions 10 (1.5) rTMS (n = 22) High frequency (10Hz), up to 20 sessions, 2500 pps (slightly outside safety guidelines) Treatment Strategy Switch Definitions Remission Ham-D₁₇ ≤ 7</p>	<p>Mean number of failed antidepressant trials: ECT: NR rTMS: NR Baseline Depression: HAM-D₁₇, mean (SD) ECT: 32.1 (5.0)* rTMS: 30.1 (4.7)* *completers analysis ECT: n = 15 rTMS: n = 20</p>	<p>HAM-D₁₇ Change, mean (SD): NR P = 0.86</p>	<p>HAM-D₁₇ Response, n (%) ECT: 6 (20) rTMS: 10 (45) P = 0.35 Remission, n (%) ECT: 3 (15) rTMS: 2 (9) P = 0.65</p>
<p>Grunhaus et al., 2003⁵⁹ 4 weeks for rTMS; ECT was at physician discretion, all reported pts included in analysis Tier 2: Did not require failure in the current episode Fair</p>	<p>ECT (n = 20) 35% bilateral, mean sessions = 10.25 (3.1) rTMS (n = 20) High frequency, 20 sessions Treatment Strategy Switch Definitions Response defined as a decrease ≥ 50% or HAM-D₁₇ score ≤ 10 and a GAF rating ≥ 60 Remission defined as HAM-D₁₇ ≤ 8</p>	<p>Number of failed antidepressant trials: % with ≥ 2 failed ECT: 60 rTMS: 65 Baseline Depression: HAM-D₁₇, mean (SD) ECT: 25.5 (5.9) rTMS: 24.4 (3.9)</p>	<p>HAM-D₁₇ Change, mean (SD) ECT: -12.3 rTMS: -11.1 P = NS</p>	<p>HAM-D₁₇ Response, n (%) ECT: 12 (60) rTMS: 11 (55) P = NS Remission, n (%) ECT: 6 (30) rTMS: 6 (30) P = NS</p>
<p>Hansen et al., 2010⁶⁰ 3 weeks, ITT Did not require failure in the current episode Tier 3—referred for ECT Fair</p>	<p>ECT (n = 30) 100% unilateral, 9 sessions rTMS (n = 30) Low frequency, 15 sessions Treatment strategy Augmentation Discontinued antiepileptics prescribed as mood stabilizers. Low-dose zopiclone or zopidem if needed for sleep Definitions Partial remission HAM-D₁₇ ≤ 12</p>	<p>Diagnosis Bipolar (%) ECT: 13.3 rTMS: 13.3 Number of failed antidepressant trials: Mean (SD) ECT: NR rTMS: NR Baseline Depression: HAM-D₁₇, median (range) ECT: 24 (16-34) rTMS: 24 (14-38)</p>	<p>HAM-D₁₇ Change, mean (SD) Reported in graph only</p>	<p>HAM-D₁₇ Response, n (%)* ECT: 17 (57) rTMS: 6 (20) Response rate difference = 0.37 (0.14-0.59) Partial Remission, n (%)* ECT: 16 (53) rTMS: 8 (27) Partial Remission rate difference = 0.26 (0.03-0.51)</p>

Table 11. Efficacy of ECT versus rTMS: Tiers 1–3 (continued)

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
McLoughlin et al., 2007, ⁶¹ Eranti et al., 2007, ⁶² and Knapp et al., 2008 ⁶³ End of treatment (at clinician's discretion for ECT group, 3 weeks in rTMS), mITT Did not require failure in the current episode Tier 3—referred for ECT Good	ECT (n = 22) 82% bilateral, mean session 6.3 (2.5) rTMS (n = 24) High frequency, 15 sessions Treatment strategy Augmentation Definitions Remission defined as ≤ 8	Diagnosis Bipolar (%) ECT: 9.1 rTMS: 8.3 Number of failed antidepressant trials: Mean (SD) ECT: 2.5 (1.4) rTMS: 2.4 (1.0) Baseline Depression: HAM-D ₁₇ , mean (SD) ECT: 24.8 (5.0) rTMS: 23.9 (7.0)	HAM-D₁₇ Change, mean (SD)* ECT: -14.1 rTMS: -5.4 P = 0.017 *only pts with post-baseline assessment ECT: n = 22 rTMS: n = 23	HAM-D₁₇ Response, n (%)* ECT: 13 (59.1) rTMS: 4 (17.4) P = 0.005 Remission, n (%)* ECT: 13 (59.1) rTMS: 4 (17.4) P = 0.005

AD = antidepressant; ECT = electroconvulsive therapy; HAM-D₁₇ = 17-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; n = number; NR = not reported; P = p-value; pps = pulses per session; pts = patients; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD-Only

One trial directly compared 4 weeks of ECT (n = 20 patients) to high-frequency rTMS (n = 22 patients) (Table 11).⁵⁸ The mean baseline HAM-D₁₇ for treatment completers was 32.1 (SD 5.0) (ECT; n = 15 patients) and 30.1 (standard deviation [SD] 4.7) (rTMS; n = 20 patients), indicating that the groups were severely depressed. ECT was initially unilateral, and it was switched to bilateral if there was no response after 2 weeks; the mean number of treatments was 10. If rTMS patients had not responded after 2 weeks, they exited the study with their last observation carried forward. The treatment strategy was a switch. ITT analyses indicated no difference between the likelihood of response with ECT versus rTMS (20% vs. 45%, P = 0.35), nor was there any difference between the likelihood of remission (15% vs. 9%, P = 0.65).

MDD/Bipolar

There were no eligible studies.

Tier 2: Patients With one or More Treatment Failures

One trial comparing ECT with rTMS was identified in Tier 2 (Table 11).

MDD-Only

One additional study was captured considering Tier 2 (Table 11).⁵⁹ This trial directly compared up to 4 weeks of ECT (n = 20 patients) with 20 sessions of high-frequency rTMS (n = 20 patients) after patients were switched from antidepressant pharmacotherapy (). Patients were severely depressed (mean HAM-D₁₇ for ECT group 25.5 [SD 5.9] and for rTMS group 24.4 [SD 3.9]). For the ECT group, patients began with unilateral treatment but were switched to bilateral treatment if response was limited. Although rTMS treatment totaled 20 sessions, ECT treatment continued until the treating physician assessed that a therapeutic response had been obtained or no further benefit was expected. The authors' analyses accounted for all patients who were randomized. At the end of treatment, ECT and rTMS patients did not differ significantly in either

depressive severity (-12.3 vs. -11.1), the response rate (60% vs. 55%), or the remission rate (30% vs. 30%).

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

Two trials comparing ECT with rTMS were identified in Tier 3 (Table 11).⁶⁰⁻⁶³

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two studies were identified for Tier 3 (Table 11).⁶⁰⁻⁶³ The first study was reported in three articles and was the only good trial involving a head-to-head comparison. Investigators used an augmentation strategy to compare outcomes following 2–3 weeks of ECT (n = 22 patients) versus 3 weeks of rTMS (n = 24) in a group of patients referred for ECT. Although failure of a prior antidepressant treatment was not a selection criterion for the study, the mean number of previous antidepressant failures was approximately 2.5 in each treatment group. The ECT group had 9.1 percent with bipolar disorder (n = 2), and the rTMS groups had 8.3 percent (n = 2) with bipolar disorder. Patients were severely depressed at baseline (mean HAM-D₁₇ = 23.9 [SD 7.0] for rTMS and 24.8 [SD 5.0] for ECT). In a modified ITT analysis, ECT patients had better outcomes in all depression domains recorded at the end of treatment. Compared to the rTMS group, those receiving ECT experienced a greater decrease in depressive severity (mean HAM-D₁₇ change -14.1 vs. -5.4, *P* = 0.017) and higher rates of both response and remission (59.1% vs. 17.4%, *P* = 0.005 for each, as all who responded also remitted).⁶⁰

A second Tier 3 study comparing ECT with rTMS was rated fair.⁶⁰ Investigators used a mostly augmentation strategy but required patients to discontinue antiepileptics (when used as mood stabilizers) and benzodiazepines. Patients referred for ECT were randomized to 3 weeks of ECT (n = 30) or rTMS (n = 30). Both groups were severely depressed at baseline (median HAM-D₁₇ = 24 [range 16–34] for ECT and 24 [14–38] for rTMS). In an ITT analysis, ECT patients had better outcomes in all depression domains recorded at the end of treatment. Compared to the rTMS group, the ECT group experienced a higher rate of response (57% vs. 20%, rate difference: 0.37 [0.14–0.59]) and partial remission (defined as HAM-D₁₇ ≤ 12: 53% vs. 27%, rate difference: 0.26 [0.03–0.51]).

Tiers 1-3: Combined Results

Although the two Tier 1 studies alone provided limited evidence of no difference between ECT and rTMS, consideration of Tiers 2 and 3 added three studies with varying results: one Tier 2 study showed no difference between ECT and rTMS and two Tier 3 studies favored ECT over rTMS.

In considering studies from all three tiers, then, two fair studies, one Tier 1 and one Tier 2, found no differences between groups in change in depressive severity, response, or remission;^{58,59} two Tier 3 studies (one good, one fair) found that ECT resulted in greater efficacy across measures.⁶¹⁻⁶³ With only four studies identified for this comparison, it is difficult to assess

what study design, participant, or treatment characteristics may have contributed to different results in both intervention efficacy and between-group comparisons.

Although the good study indicating greater efficacy for ECT was identified in Tier 3, the mean number of failed trials (N = 2.4–2.5) indicates substantial overlap with patients included in Tier 1 and Tier 2 studies.⁶¹⁻⁶³ These data were not reported for the second Tier 3 study.⁶⁰ Baseline characteristics reported in the Tier 2 study also show overlap with Tier 1 populations, with more than 60 percent of participants failing two or more antidepressant treatment trials.⁵⁹ None of the studies comparing ECT with rTMS required an antidepressant failure in the current episode. Average baseline depression scores indicate severe depression for all study populations. In the two studies allowing bipolar patients, the numbers of patients with this diagnosis were small and patients were equally distributed between treatment groups.⁶⁰⁻⁶³

Both studies finding no differences used switch strategies^{58,59} while the two studies showing greater efficacy for ECT used an augmentation strategy.⁶⁰⁻⁶³ Studies employed slightly different intervention methodologies using either high^{58,59,61-63} or low frequency rTMS⁶⁰ and unilateral⁶⁰ or bilateral^{58,59,61-63} ECT, further complicating comparisons between studies. All studies were 2 to 4 weeks in duration.

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

One trial comparing ECT with ECT plus rTMS was identified in Tier 1 (Table 12).⁶⁴

Table 12. Efficacy of ECT versus ECT plus rTMS: Tiers 1–3

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Pridmore, 2000 ⁶⁴ 2 weeks of treatment Did not require failure in the current episode Tier 1 Fair	ECT (n = 11) 100% unilateral, 6 sessions ECT plus rTMS (n = 11) ECT: 100% unilateral (day 1), plus high-frequency rTMS: (days 2-5) Repeated in week 2 Treatment Strategy Primarily augmentation (4 patients not on AD at start). ADs and mood stabilizers continued but other psychotropics discontinued Definitions Remission HAM-D ₁₇ < 9	Mean number of failed antidepressant trials: ECT: NR ECT+rTMS: NR Baseline Depression: HAM-D ₁₇ , median ECT: 30 ECT+rTMS: 28	HAM-D₁₇ Change, median ECT: -23 ECT+rTMS G2: -20 <i>P</i> = 0.6	HAM-D₁₇ Remission, n (%) ECT: 6 (54.5) ECT+rTMS G2: 6 (54.5) <i>P</i> = NR

Table 12. Efficacy of ECT versus ECT plus rTMS: Tiers 1–3 (continued)

Tier Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Chistyakov et al., 2005 ⁶⁵ 3 weeks, all reported patients included Did not require failure in the current episode Tier 3: referred for ECT Fair	ECT plus sham (n = 10) Bilateral ECT (2 days a week) plus sham rTMS (4 days a week) ECT plus rTMS (n = 12) Bilateral ECT (2 days a week) plus low frequency rTMS (4 days a week) Treatment strategy Switch	Mean number of failed antidepressant trials: ECT + sham: NR ECT+rTMS: NR Baseline Depression: HAM-D mean reported in graph only	HAM-D_{NR} Change, mean (SD) ECT+sham: NR ECT+rTMS: NR <i>P</i> > 0.05	HAM-D_{NR} Response, n (%) Overall: 19 (86) ECT+sham: NR ECT+rTMS: NR <i>P</i> = NS

AD = antidepressants; ECT = electroconvulsive therapy; HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D_{NR} = Hamilton Depression Scale; n = number; NR = not reported; NS = not significant; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD-Only

One trial directly compared 2 weeks of unilateral ECT (n = 11 patients) to a combination of 1 day of unilateral ECT followed by 4 days of high-frequency rTMS (n = 11 patients).⁶⁴ Patients were severely depressed at entry (median HAM-D₁₇ for ECT group = 30 and for ECT plus rTMS group = 28). For the majority of patients, this trial tested an augmentation strategy. However, four patients (two in each group) were not taking any antidepressant medication at study entry, and patients were allowed to continue any mood stabilizers they were taking (one in each group). ITT analyses showed no clear difference in outcomes between the two groups. Specifically, there was no difference in change in depressive severity (-23 vs. -20, *P* = 0.6) or remission rates (54.5% vs. 54.5%, *P* = not reported).

MDD/Bipolar

There were no eligible studies.

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

One trial comparing ECT with ECT plus rTMS was identified in Tier 1 (Table 12).⁶⁵

MDD-Only

Following discontinuation of antidepressant pharmacotherapy (switch strategy), a 3-week study compared 6 sessions of bilateral ECT plus 12 sessions of low frequency rTMS (n = 12) versus 6 sessions of bilateral ECT plus 12 sessions of sham rTMS (n = 10).⁶⁵ Depressive severity was not reported in text, but figures indicate HAM-D (NR) was above 40 for each group, suggesting very severe depression. The treatment strategy was a switch, and no other psychotropic medications were allowed. All patients were included in the final analysis. There was no clear difference in response rates between ECT plus rTMS versus rTMS alone (data not reported, *P* = NS).

MDD/Bipolar mix

There were no eligible studies.

Tier 1-3 Combined Results

Two fair studies found no differences between groups in change in depressive severity, response, or remission.^{64,65} With only two studies identified for this comparison, it is difficult to assess how study design, participant, or treatment characteristics may have affected treatment efficacy; furthermore, one of the two studies did not report specific data points impeding additional analysis.

Overall, studies appeared similar with the exception of tier. One study fell into Tier 1⁶⁴ and one into Tier 3⁶⁵ with no information provided regarding the average number of antidepressants failed prior to study entry for the Tier 3 study.⁶⁵ Neither study required a failure in the current episode. All patients were diagnosed with MDD and the average baseline depression scores indicate severe depression for both study populations. Dosing strategies for the combination groups in both studies were similar with patients receiving one to two sessions of ECT and four sessions of rTMS per week. ECT strategies were also similar with patients receiving 2–3 ECT sessions per week. One study used high-frequency rTMS and unilateral ECT⁶⁴; the other used low frequency rTMS and bilateral ECT.⁶⁵ Lastly, one study was 2 weeks and the other was 3 weeks.

Key Question 1a: Nonpharmacologic Interventions—Overview of Active Versus Control Comparisons

A total of 31 studies comparing an active nonpharmacologic intervention with a sham or control group were identified (Table 13), providing a total of 4 distinct comparisons: 2 comparing ECT with sham,^{67,68} 24

comparing rTMS with sham,^{18,69-92} 4 comparing psychotherapy with control,⁹³⁻⁹⁷ and 1 comparing VNS with a control group.⁹⁸ The small number of studies within some comparisons (i.e., ECT = two studies, VNS = one study, psychotherapy = four studies) and the clinical heterogeneity between study populations (e.g., severity of depression, previous antidepressant failures) did not allow for indirect comparisons of nonpharmacologic interventions.

There were no Tier 1 or Tier 2 studies comparing ECT to sham. The 2 studies comparing ECT to sham stimulation were Tier 3 studies that provided no indication of the number of prior antidepressant failures, and both reported treatment completers analyses rather than intention-to-treat. Both studies found better outcomes for the ECT group.^{67,68}

A sufficient number of studies comparing rTMS to sham stimulation allowed for some comparisons across variables. Results for Tier 1 versus Tiers 1–3 combined were consistent and generally consideration of all tiers provided more conservative point estimates with narrower

Table 13. Number of studies included by comparison and tier for KQ 1a active versus control comparisons

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT versus sham	Tier 3 (probable)	1	1
rTMS versus sham	Tier 1 (≥ 2 failures)	10	5
rTMS versus sham	Tier 2 (≥ 1 failures)	4 additional	2 additional
rTMS versus sham	Tier 3 (probable)	0	3 additional
Psychotherapy versus control	Tier 2 (≥ 1 failures)	4 additional	0
VNS versus control	Tier 1 (≥ 2 failures)	0	1 additional

MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; TAU = treatment as usual; VNS = vagus nerve stimulation

confidence intervals, suggesting that the tier results might be reasonably combined. Results for MDD-only and MDD/bipolar mix populations were in the same direction and of similar magnitude, suggesting that combining results from these two populations was reasonable. A limited number of studies within comparisons restricted analysis and prevented assessment of whether outcomes differed by depressive severity, treatment strategy, or treatment characteristics, or whether failure in the current episode was required.

Four Tier 2 MDD-only studies compared psychotherapy to control.⁹³⁻⁹⁷ For the third comparison, one good study reported in two articles^{95,96} and two fair studies^{93,97} supported greater outcomes for patients in psychotherapy compared to a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.⁹⁴ Unlike the first three studies,^{93,95-97} the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning.⁹⁴

The single study comparing VNS to a control was in a Tier 1 MDD and <20 percent bipolar population.⁹⁸ This study included patients with a higher level of treatment resistance than other studies comparing interventions in TRD populations. Considering change in HAM-D₂₄ and response outcomes only, patients in the VNS groups did not improve significantly more than patients in the control group.

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. A total of 15 different Tier 1 trials compared rTMS versus sham control for at least one of the three outcomes (Table 14). For changes in depressive severity, 14 rTMS versus sham control studies involving 497 participants provide a high degree of evidence that rTMS produces a greater decrease in depressive severity.^{18,69-73,75-82} Studies that did not report significant differences had small samples. A random effects meta-analysis of 11 Tier 1 studies indicated that rTMS produces a decrease in HAM-D depressive severity of more than 5 points relative to sham control.

Table 14. Strength of Evidence: Efficacy of rTMS versus sham—Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	14; 497	Low RCT 3 good 11 fair	Consistent	Indirect	Precise	rTMS > sham High
Response	12; 471	Low RCT 3 good 9 fair	Consistent	Indirect	Precise	rTMS > sham High
Remission	5; 223	Low RCT 2 good 3 fair	Consistent	Indirect	Precise	rTMS > sham Moderate

RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

For response rates, 12 rTMS versus sham control studies involving 471 participants provided a high degree of evidence that rTMS is more likely to produce a response than sham control.^{18,69-72,74-77,80-82} A random effects meta-analysis of 11 Tier 1 studies shows that patients receiving

rTMS are more than three times as likely to achieve a depressive response as patients receiving sham control.

For remission rates, five rTMS versus sham control studies involving 223 patients provided moderate strength of evidence that rTMS produces greater remission rates than sham (Table 14).^{18,74,77,81} A random effects meta-analysis of five Tier 1 studies shows that patients receiving rTMS are more than six times as likely to achieve remission as patients receiving sham control.

In the only other Tier 1 comparison, one good-quality VNS versus sham control study in an MDD/bipolar mix population involving 222 participants provides low evidence that neither a change in depressive severity nor response rates following VNS substantially differ from a sham control (Table 15).⁹⁸

Table 15. Strength of Evidence: Efficacy of VNS versus Sham—Tier 1

Outcome	Number of Studies; Subjects	Risk of Bias Design/Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 222	RCT Low 1 good	Unknown	Indirect	Precise	No significant difference Low
Response	1; 222	RCT Low 1 good	Unknown	Indirect	Precise	No significant difference Low
Remission	0; 0	—	—	—	—	—

RCT = randomized controlled trial; VNS = vagus nerve stimulation

Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Key Points of Active Versus Control Comparisons

Active versus control comparisons were also limited, and the small number of studies within comparisons prevented an indirect meta-analytic synthesis. Comparisons of an active nonpharmacologic intervention compared to a sham or control group were available for 4 distinct comparisons: 2 comparing ECT with sham,^{67,68} 24 comparing rTMS with sham,^{18,69-92} 4 comparing psychotherapy with control,⁹³⁻⁹⁷ and 1 comparing VNS with a control group.⁹⁸ The small number of studies within some comparisons (i.e., ECT = two studies, VNS = one study, psychotherapy = four studies) and the clinical heterogeneity between study populations (e.g., severity of depression, previous antidepressant failures) did not allow for indirect comparisons of nonpharmacologic interventions.

Electroconvulsive Therapy Versus Sham

We identified no ECT versus sham studies conducted in a Tier 1 population. Two Tier 3 studies comparing ECT with sham stimulation were identified.^{67,68} These two studies provided no indication of the number of prior antidepressant failures, and both reported treatment completers analyses rather than intention-to-treat. Both studies found greater outcomes for the ECT group.

Repetitive Magnetic Stimulation Versus Sham

For Tier 1, 10 MDD-only⁶⁹⁻⁷⁸ and 5 MDD/bipolar mix studies were identified.^{18,79-82} Three studies were deemed good quality,^{18,77,80} and the remaining studies were assessed as fair. Though some studies did not report tests of statistical significance or had very small sample sizes, evidence generally supported the benefit of rTMS over sham for a decrease in depressive symptomatology and a greater likelihood of response and remission. Results from MDD-only and from MDD/bipolar mix studies were in the same direction and of similar magnitude, and results from combining these two populations did not substantially differ from MDD-only, suggesting that combining these two populations was reasonable. Meta-analyses in TRD (Tier 1) involving both MDD-only and MDD/bipolar mix populations indicated benefit for rTMS over sham. TRD patients treated with rTMS had significantly greater decreases in depressive symptomatology (decrease in HAM-D -5.74, 95% confidence interval [CI], -7.79 to -3.68). rTMS patients were also over 3 times as likely to respond (pooled relative risk for response 3.34, 95% CI, 1.92-5.82, which translates to a number needed to treat (NNT) of 5 [95% CI, 3-10]), and over 6 times as likely to remit (pooled relative risk for remission 6.12, 95% CI, 1.89-19.80), with a NNT of 4 (95% CI, 2-20).

Consideration of all tiers together for the combined MDD and MDD/bipolar mix populations provided results consistent with those from Tier 1 alone combined but with more conservative point estimates and narrower confidence intervals. The weighted mean difference in HAM-D depressive severity was -5.92 (95% CI, -8.15 to -3.70). Because sample sizes of individual studies were small and responses to placebo varied in the small control groups, the heterogeneity was high ($I^2 = 80\%$) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. The pooled relative risk indicated that patients receiving rTMS were more than twice as likely to respond as those receiving placebo (pooled relative risk 2.68, 95% CI, 1.52-4.70), which translates into an NNT of 5 (95% CI, 4-9). Remission rates also favored rTMS. The pooled relative risk for remission was 3.73 (95% CI, 1.23-11.30), which translates to a NNT of 6 (95% CI, 3-50).

This finding of the above clinical outcomes from Tiers 1, 2, and 3 reflecting what was found with Tier 1 alone held whether the population included was MDD-only, or MDD/bipolar mix, respectively. Findings addressing the remaining key PICOTS elements were limited. Three quarters of the Tier 1 studies used an augmentation strategy^{18,69-75,79-81} while others (all MDD-only) used a switch ($n = 1$)⁷⁶ or a mixed strategy ($n = 2$).^{77,78} There was no clear difference in outcome as a function of strategy, but the limited number of comparisons prevented a firm conclusion. The consideration of additional tiers of evidence did not affect this finding.

For the few Tier 1 studies, we were unable to detect clear differences by treatment characteristics (i.e., pharmacotherapy strategy, rTMS frequency, or treatment duration) through qualitative analysis due to other potentially confounding variables resulting from study design or participant characteristics. The consideration of additional tiers of evidence did not affect this finding.

For Tier 1, 1 study did not report baseline depressive severity,⁷⁹ 1 study focused on patients with moderate disease severity,⁷² and the remaining 10 studies were on patients with severe depression. With little variation by depressive severity, we were unable to detect any differences by this variable. The consideration of additional tiers of evidence did not affect this finding.

Only three studies required a failure in the current episode, two in MDD-only^{70,72} and one in MDD/bipolar mix,⁷⁹ with no differences in outcomes apparent, but the small number of studies

prevented a more formal analysis. The consideration of additional tiers of evidence did not affect this finding.

Finally, studies used a range of rTMS and sham stimulation parameters, treatment durations, and pharmacotherapy options, thereby confounding any analysis by treatment characteristics.

Psychotherapy Versus Control

Four Tier 2 studies, all involving a form of cognitive behavioral therapy, compared psychotherapy versus control. One good study reported in two articles,^{95,96} and two fair studies^{93,97} supported better outcomes for patients in psychotherapy compared with a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.⁹⁴ Unlike the first three studies,^{93,95-97} the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning of the strategy.⁹⁴

Vagus Nerve Stimulation Versus Sham

We identified only one study comparing VNS to sham, conducted in a Tier 1 MDD/bipolar mix population.⁹⁸ The majority of measures used by this study found no difference between VNS and sham on changes in depressive severity or rates of response and remission. Since only a single study was identified for this comparison, further assessment by key variables was not possible.

Key Question 1a: Efficacy or Effectiveness of Nonpharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Active Versus Control Comparisons

Electroconvulsive Therapy Versus Sham

We identified two Tier 3 studies that compared ECT versus sham stimulation. Both studies comparing ECT to sham stimulation were in Tier 3 populations and were conducted in the early 1980s, limiting comparability to other studies in this report due to difference in antidepressant availability and study populations (e.g., no documented antidepressant failures).

Tier 1: Patients With two or More Treatment Failures

No study comparing ECT with sham in a Tier 1 population was identified.

Tier 2: Patients With one or More Treatment Failures

No study comparing ECT with sham in a Tier 2 population was identified.

Tier 3: Patients With Probable TRD

Two trials comparing ECT with sham stimulation were identified in Tier 3 (Table 16).

MDD-Only

One study in a population with “primary depressive illness” referred for ECT compared ECT (N = 13) with sham stimulation (N = 12).⁶⁷ Participants in this study had moderate depression at study entry (mean BDI, ECT 26.6 [2.8] and sham 24.1[3.5]). It is unclear what proportion of patients was on an antidepressant at study entry or had an antidepressant failure in the past. All

patients were prescribed amitriptyline during the trial. Based on a completers analysis, the ECT group had a larger mean decrease in depressive severity compared to the sham group (mean change in BDI, ECT, -15.8 versus sham: -1.9, $P < 0.002$).

MDD/Bipolar

One study in a population with “severe endogenous depression” referred for ECT compared ECT (N = 35) with sham stimulation (N = 35).⁶⁸ Participants in the study appear to have severe depression but these data are only reported in a graph. It is unclear what proportion of patients was on an antidepressant at study entry or had an antidepressant failure in the past. During the trial, patients were not prescribed an antidepressant medication. Based on a completers analysis, the ECT groups had a greater decrease in depressive severity compared with the sham group ($P < 0.01$).

Table 16. Efficacy of ECT versus sham: Tier 3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
West, 1981 ⁶⁷ 3 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	ECT (n = 13) Bilateral, 6 sessions Sham (n = 12) Treatment strategy Combination - unclear if patients taking an AD at baseline; 50 mg/d Amitriptyline during the trial	Mean number of failed antidepressant trials: ECT: NR Sham: NR Baseline Depression BDI, mean (SD) ECT: 26.6 (2.8) Sham: 24.1 (3.5)	BDI Change, mean (SD) ECT: -15.8 Sham: -1.9 $P < 0.002$ Completers ECT: N=11 Sham N=11	BDI Response NR Remission NR
Johnstone et al., 1980 ⁶⁸ 4 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	ECT (n = 35) Bilateral, 8 sessions Sham (n = 35) Treatment strategy Switch - unclear if patients taking an AD at baseline. No AD allowed during the trial	Previous manic episodes: Overall: 10% Mean number of failed antidepressant trials: ECT: NR Sham: NR Baseline Depression HAM-D ₁₇ , mean (SD) Reported in graph only	HAM-D₁₇ Change, mean (SD) Reported in graph only *ECT versus sham $P < 0.01$ Completers ECT N = 31 Sham N = 31	HAM-D₁₇ Response NR Remission NR

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tiers 1-3 Combined

Only Tier 3 studies were identified with results reported above. Given the limited data, we did not perform any quantitative syntheses.

Repetitive Magnetic Stimulation Versus Sham

Considering all tiers of evidence, 24 studies provided an rTMS versus sham comparison.^{18,69-92} Fifteen were Tier 1 studies,^{18,69-82} six were Tier 2 studies,⁸³⁻⁸⁹ and three were Tier 3 studies.⁹⁰⁻⁹² Fifteen involved an MDD-only population⁶⁹⁻⁷⁸ and nine had an MDD/bipolar mixture (< 20% with bipolar disorder).⁸³⁻⁸⁷

Tier 1: Patients With two or More Treatment Failures

Fifteen Tier 1 trials comparing rTMS with sham were identified in Tier 1.^{18,69-82}

MDD-Only

Of the 10 Tier 1 MDD-only studies identified,^{69-78,99} only 1 trial was good quality.^{77,99}

Seven of these studies tested rTMS as an augmentation strategy (Table 17).⁶⁹⁻⁷⁵ A 2-week augmentation study compared high-frequency rTMS (n = 12 patients) to sham rTMS treatment (n = 9 patients).⁶⁹ At entry, patients in the two groups were severely depressed (mean HAM-D₂₅ item scores were 34.4 in the rTMS groups and 31.7 in the control group). Analysis was modified ITT. Patients in the rTMS group had a mean change in HAM-D₂₅ severity of -11.75 versus -6.22 in the sham stimulation group (*P* = ns); the small sample size likely limited the power to detect a difference. Using the study's definition of response (> 30% in HAM-D₂₅ item), 58.3 percent of rTMS patients responded compared to 22.2 percent of the sham stimulation group (*P* = not reported). Using a more standard definition of response as 50 percent or greater decrease (which we were able to calculate from study information), 22.2 percent of rTMS patients responded.

The largest augmentation study was a 2-week trial that compared high-frequency rTMS (n = 20 patients) to a sham control (n = 20 patients).⁷⁰ Participants' depression was severe (mean HAM-D₂₁ in rTMS group = 27.1, and 25.6 in control). In an analysis of treatment completers, rTMS patients had a greater decrease in depressive severity (-7.05 vs. -1.77, *P* = 0.003). Including all participants, rTMS patients had a greater likelihood of response (25% vs. 5, *P* = NR) compared to control patients.

Table 17. Efficacy of rTMS versus Sham: Tier 1, MDD, augmentation strategies

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Boutros et al., 2002 ⁶⁹ 2 weeks Did not require failure in the current episode Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 9) Treatment strategy Augmentation Definitions Response1 definition: >30% decrease in HAM-D ₂₅ Response2 definition: ≥50% decrease in HAM-D ₂₅ **calculated from table	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₂₅ , mean (SD) rTMS: 34.4 (10.1) Sham: 31.7 (4.9)	HAM-D₂₅ Change, mean (SD) rTMS: -11.75 Sham: -6.22 <i>P</i> = NS	HAM-D₂₅ Response1, n (%) rTMS: 7 (58.3) Sham: 2 (22.2) <i>P</i> = NR Response2, n (%)** rTMS: 3 (25.0) Sham: 2 (22.2) <i>P</i> = NR
Garcia-Toro et al., 2001 ⁷⁰ 2 weeks, completers analysis Required failure in the current episode Fair	rTMS (n = 20) High frequency, 10 sessions Sham (n = 20) Treatment Strategy Augmentation	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₂₁ , mean (SD) rTMS: 27.11 (6.65) Sham: 25.6 (4.92)	HAM-D₂₁* Change, mean (SD) rTMS: -7.05 (5.66) Sham: -1.77 (3.78) <i>P</i> = 0.003 *all results based on completers (rTMS: n = 17, Sham: n = 18)	HAM-D₂₁* Response, n (%) rTMS: 5 (25) Sham: 1 (5) <i>P</i> = NR
Garcia-Toro et al., 2006 ⁷¹ 2 weeks, all reported participants included in analysis Did not require failure in the current episode Fair	rTMS-1 (n = 10) High frequency plus low frequency, 10 sessions rTMS-2 (n = 10) Same as above, but with individually assessed location Sham rTMS (n = 10) Double winged coil angled at 45 degrees Treatment strategy Augmentation	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₂₁ , mean (SD) rTMS-1: 27.30 (4.97) rTMS-2: 25.00 (4.14) Sham: 25.10 (7.28)	HAM-D₂₁ Change, mean (SD) rTMS-1: -7.2 rTMS-2: -6.9 Sham: -1.5 rTMS-1 plus rTMS-2 (-7.05) versus Sham, <i>P</i> = 0.048	HAM-D₂₁ Response, n (%) rTMS-1: 2 (20) rTMS-2: 2 (20) Sham: 0 (0) <i>P</i> = NR
Kauffmann et al., 2004 ⁷² 2 weeks Did not require failure in the current episode Fair	rTMS (n = 7) Low frequency, 10 sessions Sham (n = 5) Treatment Strategy Augmentation, pts encouraged to discontinue mood stabilizers Definitions Remission: HAM-D ₂₁ < 10	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₂₁ , mean (SD) rTMS: 21.86 (2.31) Sham: 18.20 (2.20)	HAM-D₂₁ Change, mean (SD) rTMS: -10.57 Sham: -6.31 <i>P</i> = NS	HAM-D₂₁ Response, n (%) rTMS: 4 (57) Sham: 2 (40) <i>P</i> = NR Remission, n (%) rTMS: 4 (57) Sham: 1 (20) <i>P</i> = NR

Table 17. Efficacy of rTMS versus Sham: Tier 1, MDD, augmentation strategies (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Padberg et al., 1999 ⁷³ 1 week Required failure in the current episode Fair	rTMS (n = 6) High frequency, 5 sessions Low-left rTMS (n = 6) 0.3 Hz, Left-DLPFC, 5 sessions Sham rTMS (n = 6) Treatment strategy Augmentation, 16.7% not on medication at study entry	Mean number of failed antidepressant trials (current episode): rTMS: 4.0 (2.2) Low-left rTMS: 3.2 (0.8) Sham: 3.2 (1.2) Baseline Depression HAM-D ₂₁ , mean (SD) High rTMS: 30.2 (9.5) Low-left rTMS: 26.7 (9.4) Sham: 22.2 (8.8)	HAM-D₂₁ Change, mean (SD) High rTMS: -1.7 Low-left rTMS: -5.2 Sham: -1.3 <i>P</i> = NS	HAM-D₂₁ Response: NR Remission: NR
Pallanti et al., 2010 ⁷⁴ 3 weeks Did not require failure in the current episode Fair	Low plus High rTMS (n = 20) Low then high frequency, 15 sessions rTMS (n = 20) Low frequency, 15 sessions Sham (n = 20) Treatment strategy Augmentation Definitions Remission HAM-D ₁₇ ≤ 8	Mean number of failed antidepressant trials: In lifetime rTMS1: 5.90 (1.48) rTMS2: 6.50 (1.48) Sham: 5.95 (1.67) Baseline Depression HAM-D ₁₇ , mean (SD) rTMS1: 28.75 (6.01) rTMS2: 27.95 (5.89) Sham: 29.05 (3.54)	HAM-D₁₇ Change, mean (SD) rTMS1: NR rTMS2: NR Sham: NR	HAM-D₁₇ Response, n (%) rTMS1: 4 (20%) rTMS2: 7 (35%) Sham: 2 (10%) <i>P</i> = NR NNT (95% CI) rTMS1 vs Sham 10.00 (3.13 to - 8.39) rTMS2 vs Sham 4.00 (2.01 to 328.11) Remission, n (%) rTMS1: 2 (10%) rTMS2: 6 (30%) Sham: 1 (5%) <i>P</i> = 0.064 NNT (95% CI) rTMS1 versus sham 20.00 (4.71 to -8.89) rTMS2 vs sham 4.00 (2.12 to 36.23)
Zheng et al., 2010 ⁷⁵ 4 weeks Did not require failure in the current episode Fair	rTMS (n = 19) High frequency, 20 sessions Sham (n = 15) Treatment strategy Augmentation – all patients taking escitalopram 2+ weeks before trial	Mean number of failed antidepressant trials: NR Baseline Depression HAM-D ₁₇ , mean (SD) rTMS: 24.6 (2.9) Sham: 24.6 (2.8)	HAM-D₁₇ Change, mean (SD) rTMS: -11.1 Sham: -1.7 <i>P</i> = NR	HAM-D₁₇ Response, n (%) rTMS: 12 (63.2) Sham: 1 (6.7) <i>P</i> = NR Remission NR

DLPFC = dorsolateral prefrontal cortex; HAM-D₁₇ = 17-Item Hamilton Depression Scale; HAM-D₂₁ = 21-Item Hamilton Depression Scale; HAM-D₂₅ = 25-Item Hamilton Depression Scale; Hz = hertz; n = number; NR = not reported; NS = not significant; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Another 2-week study testing augmentation compared 2 active rTMS treatments (n = 10 patients each) with each other and with 10 sessions of sham stimulation (n = 10 patients).⁷¹ Enrolled patients were severely depressed (mean HAM-D₂₁ item scores for each group between

25 and 27.3). The three groups did not appear to differ by decrease in depressive severity. However, the two active groups combined did have a greater 2-week decrease in depressive severity than the sham control group (-7.05 vs. -1.5, $P = 0.048$). Also, 2 of 10 patients in each of the active groups responded at 2 weeks, compared to no patients in the control group ($P = \text{NR}$).

A small trial compared outcomes at 2 weeks after 10 sessions of low-frequency rTMS treatment ($n = 7$ patients) with sham rTMS treatment ($n = 5$ patients).⁷² The groups had moderate depressive severity (HAM-D₂₁, 21.86 for rTMS, 18.2 for control). Although mostly an augmentation study, patients were advised to discontinue benzodiazepines and mood stabilizers. ITT analyses showed that patients receiving rTMS had a 10.57 decrease in HAM-D₂₁ compared to a 6.31 decrease for the sham stimulation group ($P = \text{NS}$). Response rates did not differ between the two groups (57% vs. 40%, $P = \text{NS}$). Investigators in this study also reported (57% vs. 20%, $P = \text{NS}$) the percentage of participants scoring less than 10 on the Hamilton Depression Scale. Again, small sample sizes may have limited the power to detect differences.

An additional small trial compared outcomes after 1 week of treatment with high-frequency rTMS ($n = 6$ patients), low-frequency rTMS to the left dorsolateral prefrontal cortex ($n = 6$ patients), or sham rTMS stimulation ($n = 6$ patients).⁷³ One treatment failure needed to have occurred in the current episode. Enrolled patients were moderately to severely depressed (mean HAM-D₂₁ score 30.2, 26.7, and 22.2 for high-frequency, low-frequency, and control groups, respectively). Patients receiving low-frequency rTMS had a significant decrease in depressive severity relative to baseline (mean HAM-D₂₁ change -1.7 for high frequency, -5.2 for low frequency to the left dorsolateral prefrontal cortex, and -1.3 for sham stimulation), but there was no difference in treatment effect between groups in this small study.

Another 3-week augmentation trial compared bilateral high- and low-frequency rTMS ($n = 20$), unilateral low-frequency rTMS ($n = 20$), and sham rTMS stimulation ($n = 20$).⁷⁴ Patients in this study were severely depressed (HAM-D₁₇ mean [SD] bilateral rTMS 28.75 [6.01] unilateral rTMS 27.95 [5.89] sham 29.05 [3.54]) and had a high number of previous antidepressant treatment failures (mean [SD] bilateral rTMS 5.90 [1.48] unilateral rTMS 6.50 [1.48] sham 5.95 [1.67]). In an ITT analysis, patients in the unilateral low-frequency rTMS but not the bilateral rTMS group were more likely to respond (NNT [95% CI] unilateral rTMS versus sham 4.00 [2.01-328.11] bilateral rTMS versus sham 10.00 [3.13 to -8.39]) and remit (NNT [95% CI] unilateral rTMS versus sham 4.00 [2.12-36.23] bilateral rTMS versus sham 20.00 [4.71 to -8.89]) from treatment compared to sham stimulation.

The last augmentation study, a 4-week trial, compared high-frequency rTMS ($n = 19$) to sham rTMS treatment ($n = 15$).⁷⁵ At baseline, participants were severely depressed (HAM-D₁₇ mean [SD] rTMS 24.6 [2.9] sham 24.6 [2.8]) and had been taking escitalopram for at least 2 weeks. In an ITT analysis, participants in the rTMS group had a greater decrease in depressive severity (rTMS -11.1 versus sham -1.7, $P = \text{NR}$) and a higher response rate (rTMS 63.2% sham 6.7%, $P = 0.001$).

Of the remaining three studies identified, one tested a switch strategy and two used a mixed strategy (Table 18). The single switch study tested was a small 2-week trial that compared high-frequency rTMS ($n = 7$ patients) to sham rTMS stimulation ($n = 8$ patients).⁷⁶ Patients were severely depressed (mean HAM-D₁₇ for the two groups was between 20 and 23). At 2-week followup, ITT analysis indicated that the decrease in depressive severity did not differ between the two groups (-8.1 for rTMS, -5.5 for sham, $P = \text{NS}$). Similarly, the rate of response did not appear to differ (28.6% vs. 12.5%, $P = \text{NR}$).

Two studies tested a mixed strategy.^{77,78} One of these trials was a good-quality 4-week study that compared 15 sessions of left-sided high-frequency rTMS (n = 35 patients) to control treatment (n = 33 patients), and was the only one to report remission rates in this tier.^{77,99} Groups enrolled were in general severely depressed (mean HAM-D₁₇ score 23.5). This mixed strategy was primarily a switch, although a substantial percentage of patients continued antidepressants (31% of rTMS group, 27% of control group) and benzodiazepines (26% and 24%, respectively). Outcomes were measured 1 week after completing the 4-week treatment, and all ITT analyses favored the rTMS group. Compared to controls, the rTMS group had a greater decrease in

Table 18. Efficacy of rTMS versus sham: Tier 1, MDD, mixed and switch strategies

Strategy Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Holtzheimer et al., 2004 ⁷⁶ 2 weeks Did not require failure in the current episode Fair	rTMS (n = 7) High frequency rTMS, 10 sessions Sham rTMS (n = 8) Treatment strategy Switch	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₁₇ , mean (SD) rTMS: 22.7 (5.3) Sham: 20.8 (6.3)	HAM-D₁₇ Change, mean (SD) rTMS: -8.1 Sham: -5.5 <i>P</i> = NS	HAM-D₁₇ Response, n (%) rTMS: 2 (28.6) Sham: 1 (14.3) <i>P</i> = NR
Avery et al., 2006 ⁷⁷ Patients treated over 4 weeks and primary endpoint 1 week after final txt Did not require failure in the current episode Good	rTMS (n = 35) High frequency, 15 sessions over 4 weeks Sham (n = 33) Treatment strategy Mixed-within group differences 31% of rTMS group and 27% of control group continued taking medications Definitions Remission definition: HAM-D ₁₇ < 10	Mean number of failed antidepressant trials: rTMS: 3.2 (2.44) Sham: 3.3 (1.72) Mean number of failed antidepressant trials (current episode): rTMS: 1.46 (0.78) Sham: 1.48 (0.67) Baseline Depression HAM-D ₁₇ , mean (SD) rTMS: 23.5 (3.9) Sham: 23.5 (2.9)	HAM-D₁₇ Change, mean (SD) rTMS: -7.8 (7.8) Sham: -3.7 (6.3) <i>P</i> = 0.002	HAM-D₁₇ Response, n (%) rTMS: 11 (31.4) Sham: 2 (6.1) <i>P</i> = 0.008 Remission, n rTMS: 7 (20.0) Sham: 1 (3.0) <i>P</i> = 0.033

Table 18. Efficacy of rTMS versus sham: Tier 1, MDD, mixed and switch strategies (continued)

Strategy Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Pascual-Leone et al., 1996 ⁷⁸ Crossover trial, 1 week Did not require failure in the current episode Fair	rTMS (n = 17) High frequency, 5 sessions Sham (n = 17) Combined data from 4 control stimulations Treatment strategy Mixed—within group differences and combination (All pts in both groups given 30 mg/d nimodipine)	Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression HAM-D ₂₁ , mean: NR	HAM-D₂₁ Change, mean: TMS: NR Sham: NR <i>P</i> < 0.0005	HAM-D₂₁ Response: NR Remission: NR

DLPFC = dorsolateral prefrontal cortex; HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D₂₁ = 21-item Hamilton Depression Scale; HAM-D₂₅ = 25-item Hamilton Depression Scale; Hz = hertz; mg/d = milligram per day; MT = motor threshold; n = number; NR = not reported; NS = not significant; *P* = p-value; pts = patients; pps = pulses per session; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt(s) = treatment(s); vs. = versus

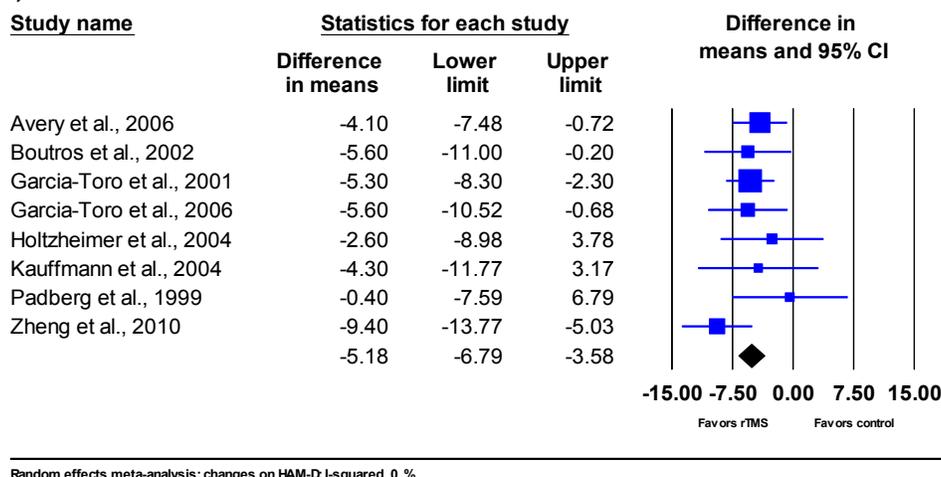
depressive severity (-7.8 vs. -3.7, *P* = 0.002), a greater response rate (31.4% vs. 6.1%, *P* = 0.008), and a greater remission rate (20.0% vs. 3.0%, *P* = 0.033).

One small mixed study used a crossover design to compare 17 TRD patients with psychotic symptoms randomized to receive different orderings of 1 high-frequency rTMS intervention and 4 different sham rTMS interventions over a 5-week period.⁷⁸ Patients had at least three episodes of depression that had been resistant to multiple medications. Baseline depressive severity was not reported. Though patients attempted to discontinue their antidepressant medication, many were unable to do so, making this strategy mixed (within group differences). All patients received nimodipine (which appears to have mood stabilizing effects) as a combination treatment with both the active rTMS and control interventions. Results suggested that the active rTMS produced greater improvement in HAM-D₂₁ scores than comparison groups (*P* < 0.0005).

Meta-Analytic Synthesis of Tier 1 MDD-Only

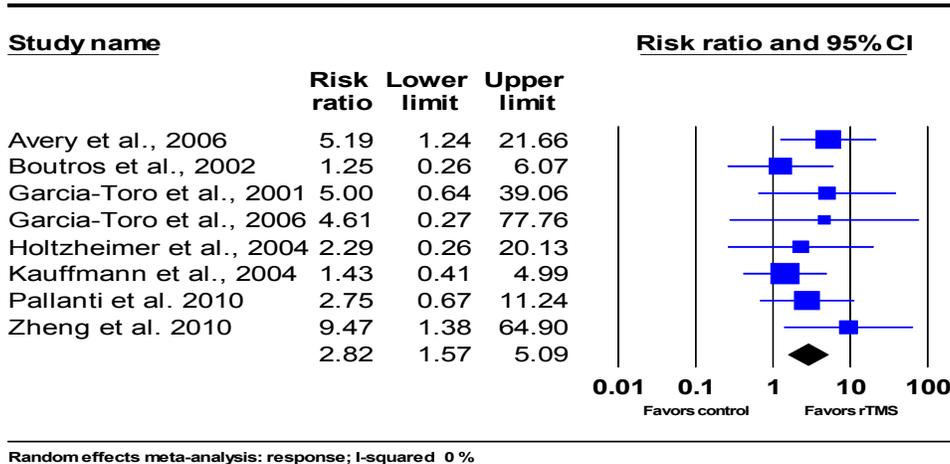
Meta-analyses supported the benefit of rTMS over sham control. The weighted mean difference in HAM-D depressive severity was -5.18 (95% CI, -6.79 to -3.58) (Figure 5).

Figure 5. Mean difference meta-analysis of changes in depressive severity comparing rTMS with sham: Tier 1, MDD



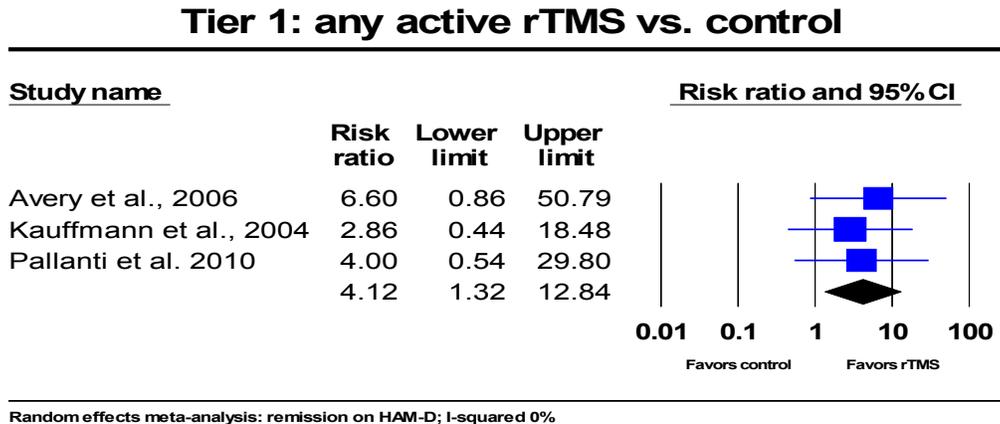
The pooled relative risk indicated that patients receiving rTMS were more than 2½ times as likely to have a treatment response as those receiving sham treatment (pooled relative risk = 2.82, 95% CI, 1.57-5.09) (Figure 6), which translates to a NNT of 5 (95% CI, 3 to 10).

Figure 6. Relative risk meta-analysis of response rates comparing rTMS with sham: Tier 1, MDD
Tier 1: any active rTMS vs. control



The pooled relative risk indicated that patients receiving rTMS were more than four times as likely to achieve remission as patients receiving sham stimulation (pooled relative risk = 4.12, 95% CI, 1.32-12.84) (Figure 7). This translates to an NNT of 6 (95% CI, 4-14).

Figure 7. Relative risk meta-analysis of remission rates comparing rTMS with Sham: Tier 1, MDD



MDD/Bipolar

For rTMS versus sham, five Tier 1 studies involving MDD/bipolar mix populations, all using augmentations strategies, were identified.^{18,79-82} These studies are summarized in Table 19 with detailed descriptions provided in the evidence tables (Appendix E).

Table 19. Efficacy of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder, augmentation strategies

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Bocchio-Chiavetto et al., 2008 ⁷⁹ Crossover, 1 week, all reported patients included in the analysis Required failure in the current episode Fair	rTMS (n = 36) Low Frequency rTMS (n = 18) 5 sessions OR, High Frequency rTMS (n = 18) 5 sessions Sham (n = 15) Treatment strategy Augmentation	Diagnosis Bipolar (%) Overall: 13.9 Mean number of failed antidepressant trials: Overall: 2.89 Baseline Depression HAM-D ₂₁ , mean (SD) rTMS: 23.19 (5.12) Sham: 24.53 (4.79)	HAM-D₂₁ Change, mean (SD) rTMS: -5.69 Sham: -3.40 P = NR	HAM-D₂₁ Response, n (%) NR Remission, n (%) NR
Fitzgerald et al., 2003 ⁸⁰ 2 weeks Did not require failure in the current episode Good	High rTMS (n = 20) High frequency, 10 sessions Low rTMS (n = 20) Low frequency, 10 sessions Sham (n = 20) Treatment strategy Augmentation Definitions Response1 definition: >20% decrease in MADRS score Response2 definition: ≥50% decrease in MADRS	Diagnosis Bipolar (%) High rTMS: 5 Low rTMS: 5 Sham: 20 Mean number of failed antidepressant trials: Overall: 5.68 (3.40) Baseline Depression MADRS, mean (SD) High rTMS: 36.05 (7.55) Low rTMS G2: 37.70 (8.36) Sham: 35.75 (8.14)	MADRS Change, mean (SD) High rTMS: -5.25 Low rTMS G2: -5.5 Sham: -0.35 High rTMS versus sham, low rTMS versus sham, P < 0.005	MADRS Response1, n (%) High rTMS: 8 (40) Low rTMS: 7 (35) Sham: 2 (10) P = 0.07 Response2, n (%) High rTMS: 0 (0) Low rTMS: 1 (5) Sham: 0 (0) P = NR

Table 19. Efficacy of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder, augmentation strategies (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
<p>Fitzgerald et al., 2006¹⁸ 6 weeks of txt (after 2 weeks, patients with < 20% decrease in score exited with LOCF) Did not require failure in current episode Good</p>	<p>High plus Low rTMS (n = 25) High frequency rTMS up to 30 sessions plus low frequency rTMS up to 30 sessions Sham (n = 25) Treatment strategy Augmentation, 23% not taking any medication at start of study Definitions Remission definition: HAM-D₁₇ < 8</p>	<p>Diagnosis Bipolar (%) rTMS: 16 Sham: 16 Mean number of failed antidepressant trials: rTMS: 5.6 (3.1) Sham: 6.2 (3.0) Baseline Depression HAM-D₁₇, mean (SD) rTMS: 22.5 (7.4) Sham: 19.8 (4.4)</p>	<p>HAM-D₁₇ rTMS: -10.2 Sham: 1.1 <i>P</i> < 0.001</p>	<p>HAM-D₁₇ Response, n (%) rTMS: 13 (52) Sham: 2 (8) <i>P</i> = 0.001 Remission (%) rTMS: 10 (40) Sham: 0 (0) <i>P</i> = 0.001</p>
<p>Su et al., 2005⁸¹ 2 weeks, completers analysis Did not require failure in the current episode Fair</p>	<p>20 Hz rTMS (n = 11) High frequency (20 Hz), 10 sessions 5 Hz rTMS (n = 11) High frequency (5 Hz), 10 sessions Sham (n = 11) Treatment strategy Augmentation Definitions Remission defined as HAM-D₂₁ < 8</p>	<p>Diagnosis Bipolar (%) 20 Hz rTMS: 10 5 Hz rTMS G2: 20 Sham G3: 20 Mean number of failed antidepressant trials: 20 Hz rTMS: NR 5 Hz rTMS G2: NR Sham G3: NR Baseline Depression HAM-D₂₁, mean (SD) 20 Hz rTMS: 23.2 (7.5) 5 Hz rTMS: 26.5 (5.2) Sham: 22.7 (4.7)</p>	<p>HAM-D₂₁* Change, mean (SD) 20 Hz rTMS: -13.4 (4.9) 5 Hz rTMS: -14.2 (6.0) Sham: -3.7 (9.3) <i>P</i> < 0.01 *n analyzed: n = 10 in each group</p>	<p>HAM-D₂₁* Response, n (%) 20 Hz rTMS: 6 (60) 5 Hz rTMS: 6 (60) Sham: 1 (10) <i>P</i> = 0.01 Remission, n (%) 20 Hz rTMS: 5 (50) 5 Hz rTMS: 5 (50) Sham: 0 (0) <i>P</i> = NR</p>
<p>Triggs et al., 2010⁸² 2 weeks Did not require failure in the current episode Fair</p>	<p>High rTMS (n = 18) High frequency, 10 sessions High right rTMS (n = 16) High frequency to the right prefrontal cortex, 10 sessions Sham left (n = 7) Sham right (n = 7) Treatment strategy Augmentation NOTE: Patients in all groups also received a social support intervention</p>	<p>Baseline Depression HAM-D₂₄, mean (SD) rTMS1: 28.2 (6.0) rTMS2: 27.2 (4.8) Sham1: 27.7(3.5) Sham2: 27.3 (2.7) Diagnosis Bipolar (%) rTMS1: 0 rTMS2: 0 Sham1: 0 Sham2: 0 Mean failed antidepressant trials NR</p>	<p>HAM-D₂₄ Change, mean (SD) rTMS1: -8.4 rTMS2: -13.5 Sham1: -5.7 Sham2: -13.9 <i>P</i> = 0.14</p>	<p>HAM-D₂₄ Response, n (%) rTMS1: 4 (22.2%) rTMS2: 5 (31.3%) Sham1: 2 (28.6%) Sham2: 4 (57.1%) <i>P</i> = NR Remission: NR</p>

HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D₂₁ = 21-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; MADRS = Montgomery-Åsberg Depression Rating Scale; n = number; NR = not reported; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt = treatment

One fair-quality trial compared 1 week of low-frequency rTMS (a group of 36, consisting of 18 who received low-frequency rTMS and 18 who received high-frequency rTMS) with 1 week of sham rTMS stimulation (involving a subgroup of 15 patients from the above group of 36 who received control treatment 8 weeks after having received rTMS).⁷⁹ Patients entered treatment severely depressed (mean HAM-D₂₁ severity 23.19 in rTMS group, 24.53 in sham group). No difference in decrease in HAM-D₂₁ item severity was identified (-5.69 in active group, -3.40 in control group, $P =$ not reported).

One good-quality trial compared three groups: one with high-frequency rTMS ($n = 20$ patients), one with low-frequency rTMS ($n = 20$ patients), and one with sham stimulation ($n = 20$ patients) following 2 weeks of treatment.⁸⁰ The three groups had MADRS scores averaging between 35 and 38, consistent with severe depression. Both the high-frequency and low-frequency groups had 5 percent bipolar patients, and the control group had 20 percent. An ITT analysis favored the two rTMS groups. Both the high-frequency (-5.25) and low-frequency (-5.5) groups had greater decrease in MADRS severity than the sham group (-0.35, $P < 0.005$ for each comparison with control). Using a definition of response as > 20 percent improvement in MADRS score, the two active groups tended to have greater rates of response (40% and 35%, respectively) compared to the sham stimulation group (10%) ($P = 0.07$ for both comparisons). Using the more standard definition of response as a 50 percent decrease, only one patient (in the low frequency group) responded by study end.

Another good-quality, 6-week study compared high-frequency rTMS plus low-frequency rTMS ($n = 25$ patients) to sham rTMS stimulation ($n = 25$ patients).¹⁸ Failure was not required in the current episode. The number of treatments depended on the presence of at least partial response. Patients entering the rTMS were severely depressed (mean HAM-D₁₇ of 22.5), while the control group was only moderately depressed (mean HAM-D₁₇ of 19.8). Sixteen percent of each group had bipolar disorder. rTMS patients had better outcomes than patients receiving sham stimulation on each response measure. Compared to control, rTMS patients had a greater improvement in HAM-D scores (-10.2 vs. -1.1, $P < 0.001$), greater response rate (52% vs. 8%, $P = 0.001$), and a greater remission rate (40% vs. 0%, $P = 0.001$).

A 2-week study compared three groups: those receiving high-frequency rTMS (20 hertz [Hz]) ($n = 11$ patients), those receiving “lower” high-frequency rTMS (5 Hz) ($n = 11$ patients), and those receiving sham rTMS treatment ($n = 10$ patients).⁸¹ Patients entering the study were severely depressed (mean HAM-D₂₁ severity for 20 Hz group 23.2, 5 Hz group 26.5, and sham group 22.7) The 20 Hz high-frequency group had 10 percent bipolar patients, and the other two group each had 20 percent with a bipolar depression. A treatment completer analysis showed that patients in the active groups had a greater decrease in HAM-D₂₁ severity (-13.4 and -14.2, respectively) than the control group (-3.7, $P < 0.01$ for each comparison). Similarly, response favored the two rTMS groups (60% for each vs. 10% for the sham stimulations comparison, $P = 0.01$ for both). Finally, both rTMS treatments had greater remission rates (50%) than the sham control group, which had no remitters ($P =$ not reported).

A fifth augmentation study compared high-frequency rTMS to the left dorsolateral prefrontal cortex ($n = 18$) and high-frequency rTMS to the right dorsolateral prefrontal cortex ($n = 16$), with sham rTMS treatments to the same locations (left $n = 7$, right $n = 7$).⁸² Unlike other studies comparing rTMS and sham stimulation, in this study all patients also received a social support intervention. At baseline, patients were severely depressed (HAM-D₂₄ mean [SD] high rTMS 28.2 [6.0], high right rTMS 27.2 [4.8], sham left 27.7 [3.5], sham right 27.3 [2.7]), and only two patients in the high right rTMS group had bipolar disease (high right rTMS 12.5%, all other

groups 0%). Patients in all groups had a decrease in depressive severity (HAM-D₂₄ mean high rTMS -8.4, high right rTMS -13.5, sham left -5.7, sham right -13.9, $P = \text{NR}$), but patients in the active rTMS groups were not more likely to respond to treatment compared to those in the sham group (high rTMS 22.2%, high right rTMS 31.3%, sham left 28.6%, sham right 57.1%, $P = 0.14$). It is possible that the inclusion of a social support intervention may have muffled the effects of rTMS in this study.

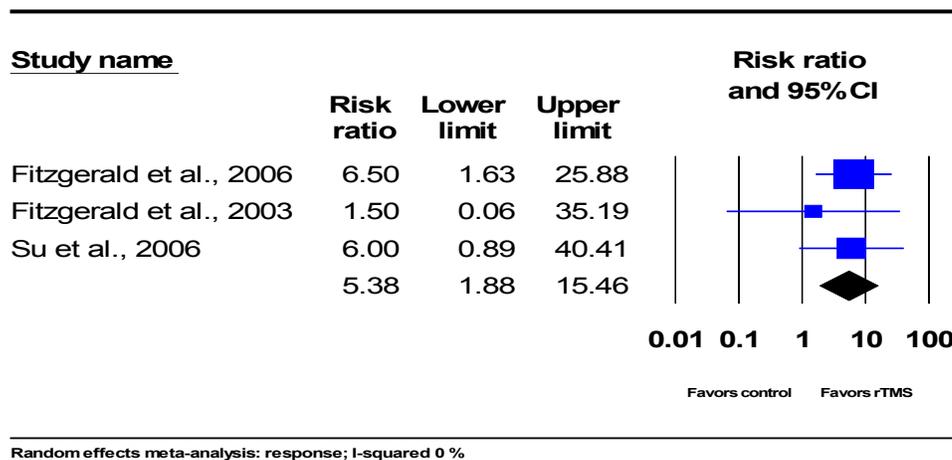
Meta-Analytic Synthesis of Tier 1 MDD/Bipolar mix Outcomes

We were able to quantitatively synthesize outcomes from four of the five studies within an MDD/bipolar mix Tier 1 population.^{18,79-82} The fifth study, an outlier, was excluded from the analysis.⁸² Though the rTMS intervention in this study used similar stimulation parameters to others in this category, an extensive supportive social intervention distinguished it from the other trials. This additional co-intervention may have diminished the comparative efficacy of rTMS and sham stimulation. Based on these concerns and the heterogeneity introduced when this study was included, we excluded this study from the meta-analyses.

For changes in depressive severity involving the three studies using HAM-D as an outcome, patients receiving rTMS on average had approximately a 7-point greater decrease relative to sham control (-7.25, 95% CI, -10.87 to -3.64). Because sample sizes were small and responses to placebo varied in the small control groups, the heterogeneity was high ($I^2 = 90\%$) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

The pooled relative risk (HAM-D or MADRS) indicated that patients receiving rTMS were more than five times as likely to have a treatment response as those receiving sham treatment (5.38, 95% CI, 1.88-15.46) (Figure 8), which translates to an NNT of 3 (95% CI, 1-14).

Figure 8. Relative risk meta-analysis of response rates comparing rTMS versus sham: Tier 1, MDD/≤ 20 percent bipolar disorder



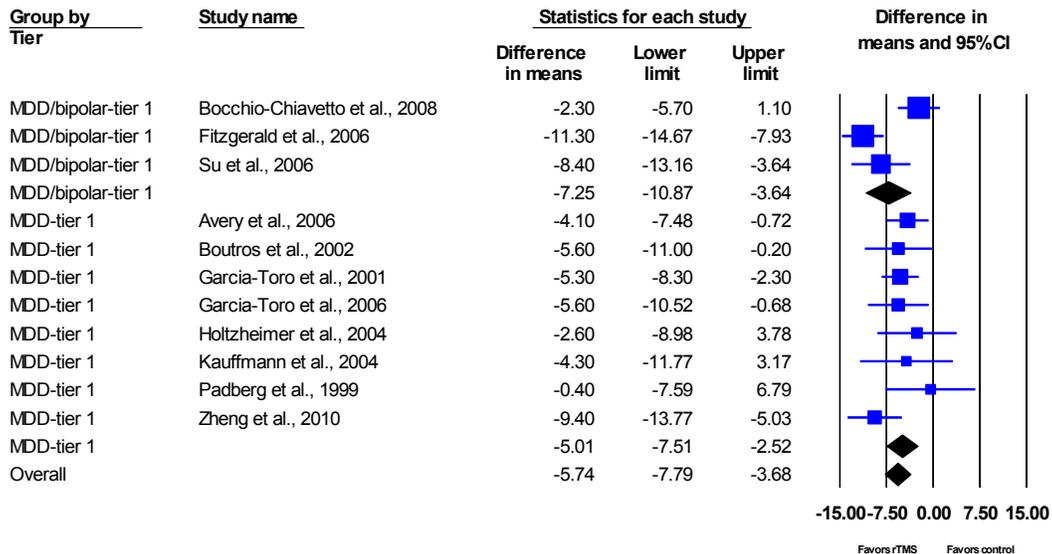
We were unable to quantitatively synthesize remission rates because only two studies in this population reported this outcome; both studies indicated greater absolute remission rates for rTMS compared with sham.^{18,81}

Tier 1 MDD and MDD/Bipolar Combined

Meta-analyses combining TRD studies (Tier 1) from both MDD and MDD/bipolar mix populations continued to support the benefit of rTMS over sham control. The mean difference in HAM-D depressive severity was -5.74 (95% CI, -7.79 to -3.68) (Figure 9). The pooled relative risk indicated that patients receiving rTMS were more than three times as likely to respond as those receiving placebo (pooled relative risk 3.34, 95% CI, 1.92 to 5.82) (Figure 10), which translates into a NNT of 5 (95% CI, 3-10). Remission rates also favored rTMS. The pooled relative risk for remission was 6.12 (95% CI, 1.89 to 19.80), which translates to a NNT of 4 (95% CI, 2-20) (Figure 11).

MDD/bipolar mix point estimates tended to be slightly higher than those for MDD-only, but confidence intervals overlapped, suggesting no clear difference. Indeed, combining the two populations did not affect the direction nor did it substantially impact the magnitude of the results, and the combined results were consistent with what was reported for the Tier 1 syntheses separately.

Figure 9. Mean difference meta-analysis of changes in depressive severity comparing rTMS versus sham: Tier 1



Random effects meta-analysis: changes on HAM-D; I-squared 55 %

Figure 10. Relative risk meta-analysis of response rates comparing rTMS versus sham: Tier 1

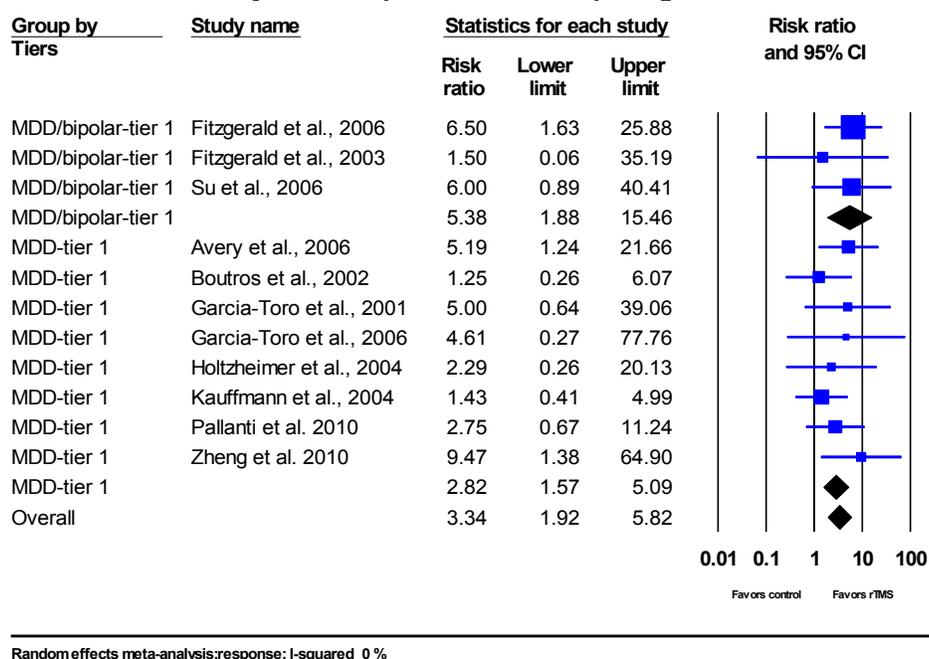
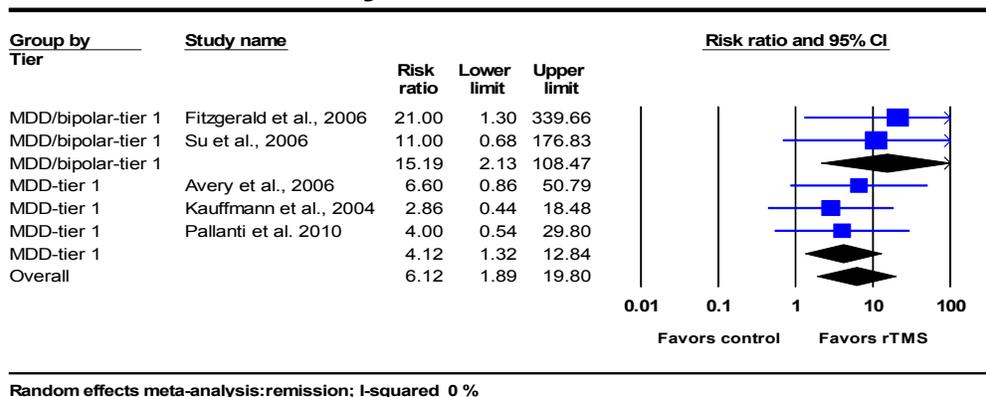


Figure 11. Relative risk meta-analysis of remission rates comparing rTMS versus sham: Tier 1

Tier 1: any active rTMS vs. control



Tier 2: Patients With one or More Treatment Failures

Consideration of Tier 2 provided six additional studies: four MDD-only studies (reported in six articles)⁸³⁻⁸⁷ and two additional MDD/bipolar mix studies.^{88,89}

MDD-Only

Consideration of Tier 2 study populations added four additional studies reported in five articles.⁸³⁻⁸⁷ Two trials were rated good quality, while two were rated fair quality. All employed switch strategies, and evaluated rTMS versus sham stimulation in patients with one or more treatment failures (Table 20).

A large study, rated to be of good quality, compared up to 6 weeks of high frequency (n = 93) with sham rTMS stimulation (n = 98).⁸³ On average, patients in the trial had moderate to severe depression (mean HAM-D₂₄ rTMS 26.3 sham 26.5) and had three antidepressant failures

in their lifetime (rTMS 3.34 sham 3.28). Using a modified ITT analysis, patients in the rTMS group had a greater decrease in depressive severity (at week 3, rTMS -4.7 sham -3.3, $P = 0.06$) and higher rates of response (OR, 4.6 [95% CI, 1.47-14.42]) and remission (OR, 4.18 [95% CI, 1.32-13.24]).

A brief 1-week trial compared high-frequency rTMS ($n = 10$ patients) to sham stimulation ($n = 10$ patients).^{84,85} Enrolled patients had moderate to severe depression (mean HAM-D severity approximately 23 in each group). Whether the analysis conducted was ITT or treatment completer was not clear. Results demonstrated no difference between the rTMS and sham groups in the decrease of depressive severity (-9 vs. -6.5, $P > 0.66$), the rate of response (30% in each), or the rate of remission (20% in each).

The largest trial the second good-was a 4-week study comparing high-frequency rTMS ($n = 165$ patients) to sham stimulation ($n = 160$ patients).⁸⁷ Patients were required to have at least one but not more than four failed adequate antidepressant treatments in this or the most recent episode or to have failed to tolerate four adequate lifetime medication trials. The groups participating were severely depressed (mean HAM-D₁₇ approximately 23). A modified ITT analysis involving 301 patients at 6 weeks favored rTMS, which showed a greater decrease in depressive severity (mean HAM-D₁₇ decrease of 5.5 versus 3.3, $P = 0.005$) and a greater response rate (24.5% vs. 13.7%, $P < 0.05$), while there was a trend toward greater remission rates with rTMS (15.5% vs. 8.9%, $P = 0.065$).

The fifth trial compared 2 weeks of rTMS stimulation among four groups: high-frequency rTMS ($n = 10$ patients), low frequency left-sided rTMS ($n = 10$ patients), low frequency right-sided rTMS ($n = 10$ patients), and sham control ($n = 15$ patients).⁸⁶ All patients had been referred for ECT following treatment failure of an adequate course of an antidepressant medication. The groups involved were severely depressed (mean HAM-D₂₁ item ranged between 27 and 28 for each group). It was unclear whether the analysis conducted was ITT or treatment completers. For each outcome, the high-frequency rTMS and the low-frequency rTMS groups appeared to produce better outcomes than the low frequency left-sided rTMS and sham groups. The high left-sided rTMS and low right-sided rTMS groups produced a greater decrease in depressive severity than the low left rTMS or sham group (mean change in HAM-D₂₁ high rTMS > low left rTMS + sham and low right rTMS > low left rTMS + sham, $P < 0.0005$). Response rates (50% and 50% vs. 0% and 0%, $P =$ not reported) and remission rates (30% and 10% vs. 0% and 0%; $P =$ not reported) also appeared higher in the same two groups.

Table 20. Efficacy of rTMS versus sham: Tier 2, MDD

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
George et al., 2010 ⁸³ Up to 6 weeks, mITT Did not require failure in the current episode Good	rTMS (n = 92*) High frequency, 15 sessions Sham (n = 98*) *mITT (N randomized = 199) Treatment strategy Switch Definitions Remission definition HAM-D ₂₄ < 10 at two consecutive visits	Mean failed antidepressant trials: Current/lifetime rTMS: 1.62/3.34 Sham: 1.41/3.28 Baseline Depression HAM-D ₂₄ , mean (SD) rTMS: 26.3 (5.0) Sham: 26.5 (4.8)	HAM-D₂₄ At 3 weeks Change**, mean (SD) rTMS: -4.7 Sham: -3.1 **observed rTMS n = 83 Sham n = 91 95% CI effect estimate (adjusted) -4.23 to 0.10, P = 0.06	HAM-D₂₄ Response*, n (%) rTMS: 14 (15.2) Sham: 5 (5.1) OR, 4.6 (95% CI, 1.47-14.42) Remission*, n (%) rTMS: 13 (14.1) Sham: 5 (5.1) OR, 4.18 (95% CI, 1.32-13.24)
Manes et al., 2001 ⁸⁴ and Moser et al., 2002 ⁸⁵ 1 week, all reported patients included in analysis Did not require failure in the current episode Fair	rTMS (n = 10) High frequency, 5 sessions Sham (n = 10) Treatment strategy Switch Definitions Response definition: 50% reduction in HAM-D and no longer met DSM criteria for major or minor depression Remission definition: HAM- D < 8	Diagnosis Major Depression,% rTMS: 80 Sham: 100 Dysthymia,% rTMS: 20 Sham: 0 Mean number of failed antidepressant trials: rTMS: 4 (2.3) Sham: 4 (1.2) Baseline Depression HAM-D NR, mean (SD) rTMS: 22.7 (5.2) Sham: 22.7 (7.1)	HAM-D NR Change, mean (SD) rTMS: -9 Sham: -6.5 P >0.66	HAM-D NR Response, n (%) rTMS: 3 (30) Sham: 3 (30) P = NS Remission, n (%) rTMS: 2 (20) Sham: 2 (20) P = NR
Stern et al., 2007 ⁸⁶ 2 weeks, all reported patients included in analysis Required failure in the current episode Fair	rTMS -1(n = 10) High frequency, 10 sessions rTMS -2(n = 10) Low frequency (1 Hz), Left- DLPFC, 10 sessions rTMS-3 (n = 10) Low frequency, 10 sessions Sham (n = 15) Treatment strategy Switch Definitions Remission definition HAM-D ₂₁ ≤ 10	Mean number of failed antidepressant trials: rTMS-1: NR rTMS-2: NR rTMS-3: NR Baseline Depression HAM-D ₂₁ , mean (SD) rTMS-1: 27.8 (3.2) rTMS-2: 27.6 (3.9) rTMS-3: 27.9 (3.8) Sham: 27.4 (2.9)	HAM-D₂₁ Change, mean (SD) rTMS-1: -12.7 rTMS-2: 0.0 rTMS-3: -12.1 Sham: -0.7 rTMS-1 > rTMS-2 + sham and rTMS > rTMS-2 + sham, P < 0.0005	HAM-D₂₁ Response, n (%) rTMS-1: 5 (50) rTMS-2: 0 (0) rTMS-3: 5 (50) Sham: 0 (0) P = NR Remission, n (%) rTMS-1: 3 (30) rTMS -2: 0 (0) rTMS -3: 1 (10) Sham: 0 (0) P = NR

Table 20. Efficacy of rTMS versus sham: Tier 2, MDD (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
O'Reardon, 2007 ⁸⁷ 6 weeks; at week 4, patients not responding left study with LOCF, mITT Did not require failure in the current episode Good	rTMS (n = 165) High frequency, up to 30 sessions Sham (n = 160) Treatment strategy Switch Definitions Remission definition: HAM-D ₁₇ ≤ 7	Mean number of failed antidepressant trials: rTMS: 1.6 Sham: 1.6 Baseline Depression HAM-D ₁₇ , mean (SD) rTMS: 22.6 (3.3) Sham: 22.9 (3.5)	HAM-D₁₇* Change, mean (SD) rTMS:-5.5 Sham:-3.3 $P = 0.005$ *Results based on rTMS: n = 155 Sham: n = 146	HAM-D₁₇* Response, n (%) rTMS: 38 (24.5) Sham: 20 (13.7) $P < 0.05$ Remission, n (%) rTMS: 24 (15.5) Sham: 13 (8.9) $P = 0.065$

DLPFC = dorsolateral prefrontal cortex; DSM = Diagnostic and Statistical Manual; HAM-D = Hamilton Depression Scale; HAM-D₂₁ = 21-item Hamilton Depression Scale; Hz = hertz; LOCF = last observation carried forward; mITT = modified intention to treat; n = number; NR = not reported; P = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar

Consideration of Tier 2 added two MDD/bipolar mix studies. The first was a 2-week switch study comparing high-frequency rTMS (n = 10 patients) to sham rTMS treatment (n = 10 patients).⁸⁸ This study is summarized in Table 21, with a detailed description provided in the evidence tables (Appendix E). All patients had at least one treatment failure following an adequate antidepressant trial during the current episode except one, who had previously received ECT and had proven treatment resistant to antidepressants in the past). Patients entered into the study with a severe degree of depression (approximately 37 on the HAM-D₂₅ item scale in each group). As with the Tier 1 group, the rTMS group had a mean HAM-D₂₅ decrease of 14 compared to a decrease of 0.2 in the control group ($P < 0.01$). Response rates also favored rTMS (10% vs. 0%, $P = 0.09$).

Over a duration of 3 weeks, the second study compared the combination of high-frequency rTMS plus escitalopram (n = 25 patients) with sham rTMS plus escitalopram (n = 24 patients) in patients who had discontinued their previous antidepressant pharmacotherapy (failed within the current episode).⁸⁹ Those participating were moderately to severely depressed (mean HAM-D₁₇ was 25.3 [SD 3.0] in rTMS group and 24.7 [SD 3.2] in the sham control). Authors conducted a modified ITT analysis. Mean depressive severity change was -8.9 in the rTMS escitalopram group and -5.6 in the sham alone group. This comparison favored rTMS plus pharmacotherapy over pharmacotherapy alone with the authors reporting an effect size of 0.78 (95% CI, 0.18 to 1.39).

Table 21. Efficacy of rTMS versus sham: Tier 2 MDD and ≤ 20 percent bipolar disorder

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population characteristics	Change in depressive symptoms	Response Remission
Berman et al., 2000 ⁸⁸ 2 weeks Did not require failure in the current episode Fair	rTMS (n = 10) High frequency, 10 sessions Sham (n = 10) Treatment strategy Switch	Diagnosis Bipolar (%) rTMS: 0 Sham: 10 Mean number of failed antidepressant trials: rTMS: 5 Sham: 3.5 (plus 1 failed augmentation medication each) Baseline Depression HAM-D ₂₅ , mean rTMS: 37.1 Sham: 37.3	HAM-D₂₅ Change, mean* (SEM) rTMS: -14.0 (3.7) Sham: -0.2 (4.1) <i>P</i> < 0.01 *adjusted mean decreases based on best fit slopes	HAM-D₂₅ Response, n (%) rTMS: 1 (10) Sham: 0 (0) <i>P</i> = 0.09
Bretlau et al., 2008 ⁸⁹ 3 weeks, mITT Required failure in the current episode. Fair	rTMS (n = 25) High frequency, 15 sessions over 3 weeks Sham (n = 24) 20 mg escitalopram Treatment Strategy Combination all patients received 20 mg escitalopram	Previous manic episodes: rTMS: 4.5% Sham: 13.0% Mean number of failed antidepressant trials (current episode): rTMS: 2.8 (0.9) Sham: 2.5 (0.9) Baseline Depression: HAM-D ₁₇ , mean* (SD) rTMS: 25.3 (3.0) Sham: 24.7 (3.2) *based on rTMS: n = 22 Sham: n = 23	HAM-D₁₇ Change, mean* (SD) rTMS: -8.9 Sham: -5.6 Effect size: 0.78 (0.18-1.39)*	HAM-D₁₇ Response, n (%) NR Remission, n (%) NR

HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D₂₅ = 25-item Hamilton Depression Scale; mITT = modified intention to treat; n = number; rTMS = repetitive transcranial magnetic stimulation; SEM = standard error of measurements

Tier 3: Patients With Probable TRD

Three trials comparing rTMS with sham stimulation were identified in Tier 3 (Table 22).

MDD-Only

There were no eligible studies.

MDD/Bipolar

Three small studies compared rTMS versus a sham control; these studies are summarized in Table 22 and described in detail in the evidence tables (Appendix E). Two studies reported significantly better outcomes for rTMS and the third identified a trend in this direction. Results did not vary by strategy. Study duration did not appear to affect outcomes.

Table 22. Efficacy of rTMS versus sham: Tier 3 MDD and ≤ 20 percent bipolar disorder

Author, year Study Design Primary endpoint(s) Quality Tier	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
<p>Bortolomasi et al., 2006⁹⁰ 1 week, all reported patients included in analysis Did not require failure in the current episode Tier 3—"drug resistance" not defined Fair</p>	<p>rTMS (n = 12) High frequency, 5 sessions Sham (n = 7) Treatment strategy Augmentation</p>	<p>Diagnosis Bipolar (%) rTMS: 16.7 Sham: 14.3 Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression: HAM-D₂₄ rTMS: 25.17 Sham: NR</p>	<p>HAM-D₂₄ Change, mean (SD) rTMS: -13.84 Sham: NR <i>P</i> = data NR but text states not significant</p>	<p>HAM-D₂₄ Response, n (%) NR Remission, n (%) NR</p>
<p>George et al., 1997⁹¹ Crossover, 2 weeks Tier 3—all patients had 1+ implied current episode failures Fair</p>	<p>rTMS (n = 12) High frequency, 10 sessions Sham (n = 12) Treatment strategy Mixed-within group difference Patients discontinued their (failed) ADs with the exception of 3 patients who were partial responders</p>	<p>Diagnosis Bipolar (%) Overall: 8.3 Mean number of failed antidepressant trials: Overall: 13.4 Baseline Depression: HAM-D₂₁ Overall: 28.5 (4.2)</p>	<p>HAM-D₂₁ Change, mean (SD) rTMS: -5.25 Sham: +3.33 <i>P</i> < 0.03</p>	<p>HAM-D₂₁ Response, n (%) NR Remission, n (%) NR</p>

Table 22. Efficacy of rTMS versus sham: Tier 3 MDD and ≤ 20 percent bipolar disorder (continued)

Author, year Study Design Primary endpoint(s) Quality Tier	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Moller, 2006 ⁹² Crossover, within 1 week of completing 1 week of txt Did not require failure in the current episode. Tier 3—TRD not defined Fair	rTMS (n = 10) High frequency, 5 sessions Sham (n = 10) Treatment strategy Augmentation	Diagnosis Bipolar (%) Overall: 20 Mean number of failed antidepressant trials: rTMS: NR Sham: NR Baseline Depression: HAM-D ₁₇ Median (range) rTMS: 20 (13-37) Sham: 16 (7-31)	HAM-D₁₇ Change (median) rTMS: -7 Sham: -1 <i>P</i> = 0.075	HAM-D₁₇ Response, n (%) NR Remission, n (%) NR

Ads = antidepressants; ; HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D₂₁ = 21-item Hamilton Depression Scale; HAM-D₂₄ = 24-item Hamilton Depression Scale; n = number; NR = not reported; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; TRD = treatment-resistant depression; txt = treatment

With the exception of a control arm in one study, all groups were severely depressed. All studies used high-frequency rTMS and none required treatment failure in the current episode.

One study compared 5 sessions per week of high-frequency rTMS (n = 12 patients) to sham stimulation (n = 7 patients).⁹⁰ The authors indicated that patients needed to meet criteria for “drug resistance,” but this definition was not provided. Patients enrolled were depressed (mean HAM-D₂₄ for rTMS group = 25.17). Those receiving rTMS had a greater decrease in mean HAM-D₂₄ severity than those in the control group (the text states that the difference is statistically significant, but it does not report the test).

The other augmentation trial was a small randomized crossover study that compared patients (n = 10) receiving 1 week of high-frequency versus sham stimulation.¹⁰⁰ Patients were referred to the study because their depression was “drug resistant,” and the authors note that “various antidepressants had previously been tried without adequate success.” On average, patients entering the study were moderately to severely depressed (median HAM-D₁₇ for sham = 16 [moderate] and for rTMS = 20 [severe]). Outcomes suggested benefit for rTMS as measured by mean change in depressive severity (-7 vs. -1), but in this small sample this difference was insignificant (*P* = 0.075).

A third trial tested a mixed strategy that also used a crossover design. The study (n = 12 patients) compared 2-week outcomes for patients who received, in randomized order, 2 weeks of high-frequency rTMS and 2 weeks of sham rTMS stimulation.⁹¹ All patients still met criteria for a major depressive episode despite treatment with an antidepressant, suggesting failure in the current episode. Patients entering the trial were severely depressed (mean HAM-D₂₁ score = 28.5). Results from an ITT analysis favored active treatment; the rTMS group had a greater mean change in depressive severity (-5.25 vs. + 3.33, *P* < 0.03).

Tiers 1-3 Combined

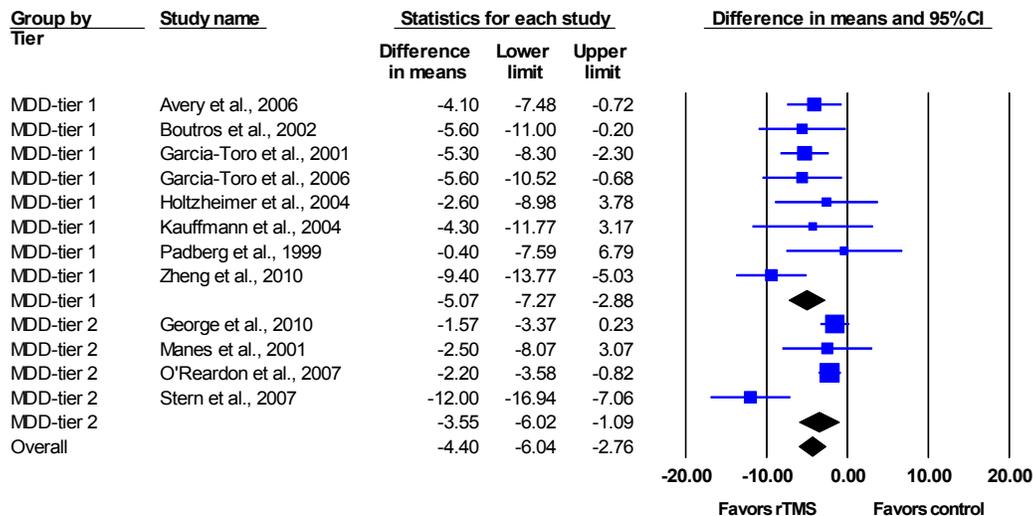
Twenty-four studies comparing rTMS with sham rTMS stimulation were identified.^{18,69-82,84-88,90,91} The majority of studies for this comparison found that rTMS resulted in significantly greater efficacy as measured by change in depressive severity, response, and remission. Other studies did not report tests of statistical significance or were underpowered to detect differences between groups. Differences in efficacy by tier and inclusion of patients with bipolar disorder were assessed via stratified meta-analyses.

Meta-Analytic Synthesis of Outcome in an MDD-Only Population (Tiers 1, 2, and 3 Combined)

Meta-analyses combining studies from only Tier 1 and Tier 2 studies (as there were no Tier 3 studies identified) supported the benefit of rTMS over sham control and were consistent with Tier 1 analyses. The weighted mean difference in HAM-D depressive severity was -4.40 (95% CI, -6.04 to -2.76) (Figure 12). The pooled relative risk indicated that patients receiving rTMS were approximately twice as likely to respond as those receiving placebo (pooled relative risk 2.18, 95% CI, 1.47 to 3.22) (Figure 13), which translates into a NNT of 6 (95% CI, 4–10). Pooled relative risk for remission rates only slightly favored rTMS at 2.37 (95% CI, 1.20 to 4.69) (Figure 14).

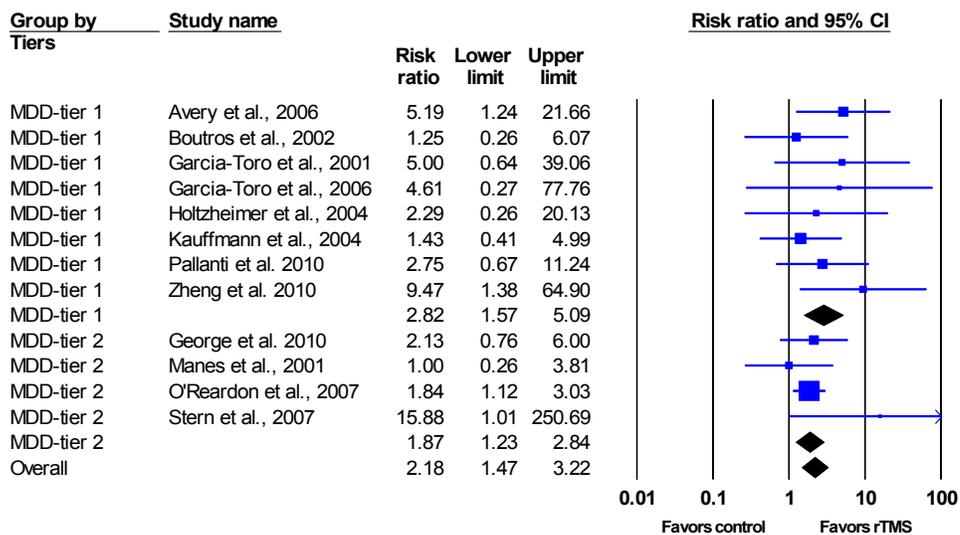
Combining these three tiers for MDD-only populations provided a more conservative point estimate and a narrower confidence interval for each of the three outcomes than the quantitative syntheses for Tier 1 MDD-only.

Figure 12. Mean difference meta-analysis of changes in depressive severity comparing rTMS with sham: Tiers 1 & 2, MDD



Random effects meta-analysis: changes on HAM-D; I-squared 63 %

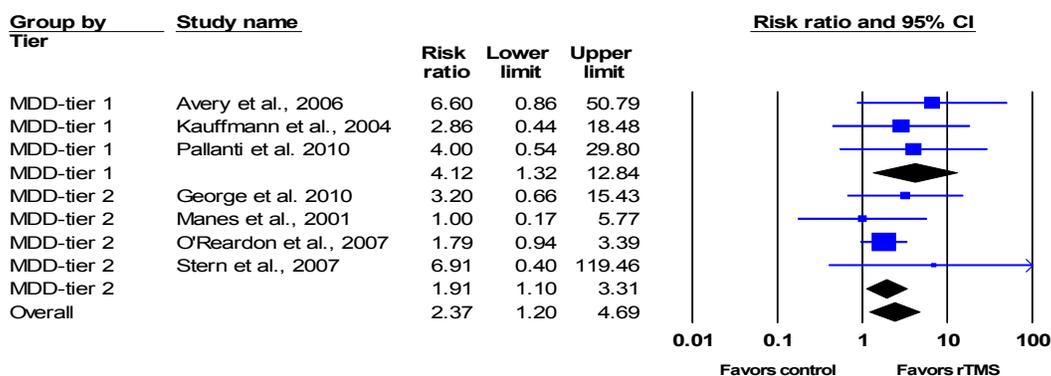
Figure 13. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, MDD



Random effects meta-analysis: response; I-squared 0 %

Figure 14. Relative risk meta-analysis of remission rates comparing rTMS with sham: Tiers 1 & 2, MDD

Tier 1 & tier 2 : any active rTMS vs. control



Random effects meta-analysis: remission on HAM-D; I-squared 0%

Meta-Analytic Synthesis of MDD/Bipolar mix Outcomes (Tiers 1, 2, and 3 Combined)

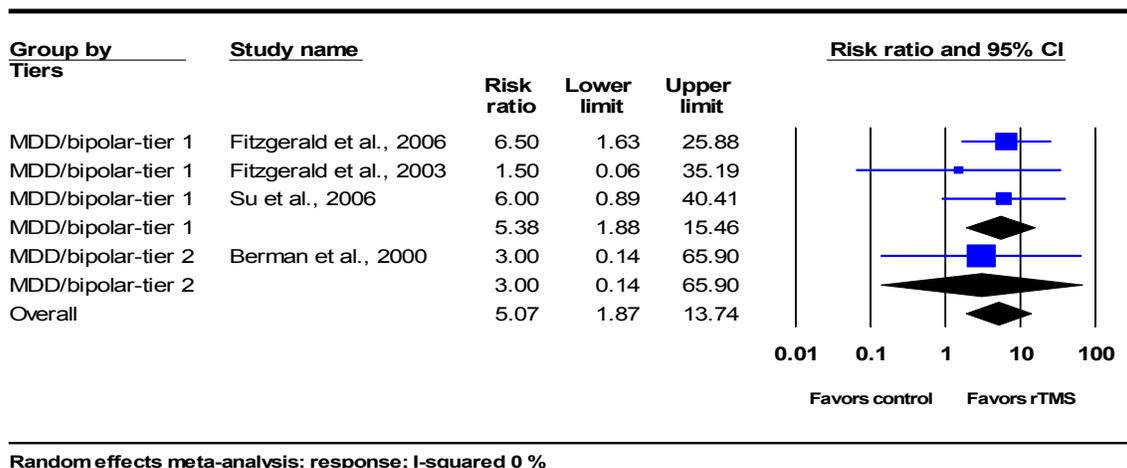
Meta-analyses combining studies from all tiers in this population allowed for comparisons of response and remission in Tier 1 and Tier 2 studies and for change in depressive severity within all three tiers. Combining this data with Tier 1 results continued to support benefit for rTMS. For changes in depressive severity as measured by the mean HAM-D difference, patients receiving rTMS on average had a decrease of nearly 8 points relative to sham control (-7.73, 95% CI, -13.31 to -2.14). Because sample sizes were small and responses to placebo varied in the small control groups, the heterogeneity was high ($I^2 = 90\%$) and our estimates are uncertain with

respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

Response rates also favored rTMS, with rTMS groups being more than five times as likely to achieve response (random effects relative risk 5.07, 95% CI, 1.87 to 13.74) (Figure 15), leading to a NNT of 3 (95% CI, 1-14). We were unable to quantitatively synthesize remission results due to the small number of studies reporting this outcome.

Compared to the meta-analytic synthesis of Tier 1 MDD/bipolar mix studies, the combination of Tiers 1–3 produced nearly identical point estimates for change in depressive severity and response rate and narrower confidence intervals.

Figure 15. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, MDD/≤ 20 percent bipolar disorder



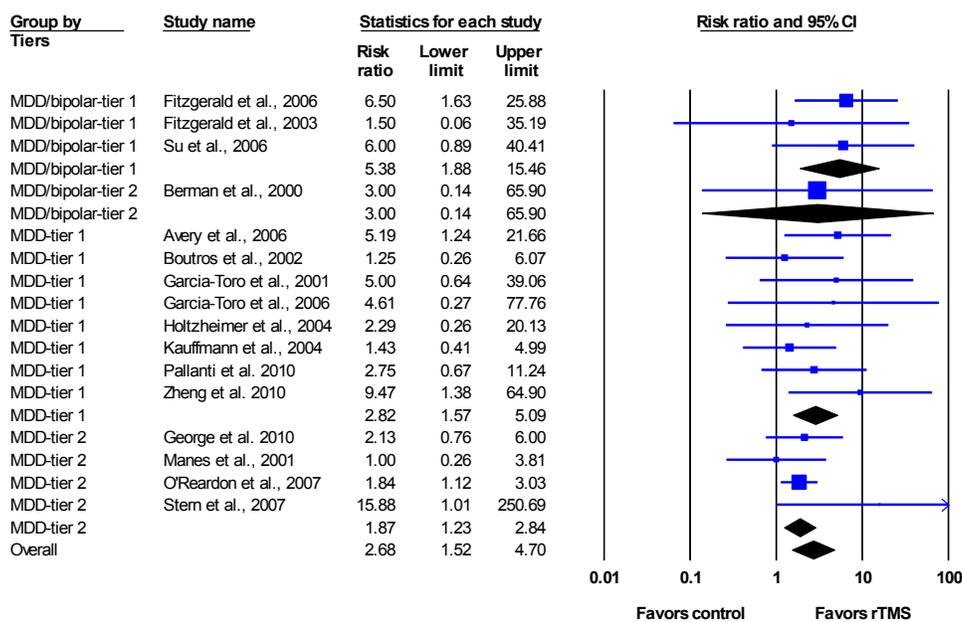
Meta-Analytic Synthesis of MDD and MDD/Bipolar mix Outcomes (Tiers 1, 2, and 3 Combined)

Meta-analyses combining studies from all tiers involved and including both MDD and MDD/bipolar mix populations continued to support the benefit of rTMS over sham control and were consistent with Tier 1 combined analyses. Most studies showed a significantly greater decrease in depressive severity in the rTMS group. The weighted mean difference in HAM-D depressive severity was -5.92 (95% CI, -8.15 to -3.70). Because sample sizes of individual studies were small and responses to placebo varied in the small control groups, the heterogeneity was high ($I^2 = 80\%$) and our estimates are uncertain with respect to the magnitude of changes on the HAM-D. Given this uncertainty, we are not including the forest plot.

The pooled relative risk indicated that patients receiving rTMS were more than twice as likely to respond as those receiving placebo (pooled relative risk 2.68, 95% CI, 1.52-4.70) (Figure 16), which translates into a NNT of 5 (95% CI, 4-9). Remission rates also favored rTMS. The pooled relative risk for remission was 3.73 (95% CI, 1.23-11.30), which translates to an NNT of 6 (95% CI, 3-50) (Figure 17).

Compared to Tier 1 syntheses of MDD and MDD/bipolar populations combined, consideration of all three tiers provided more conservative point estimates and narrower confidence intervals for each outcome. Indeed, the meta-analytic results for MDD and MDD/bipolar mix for all tiers combined were most nearly identical to results for the Tier 1 MDD-only group, our main population of interest.

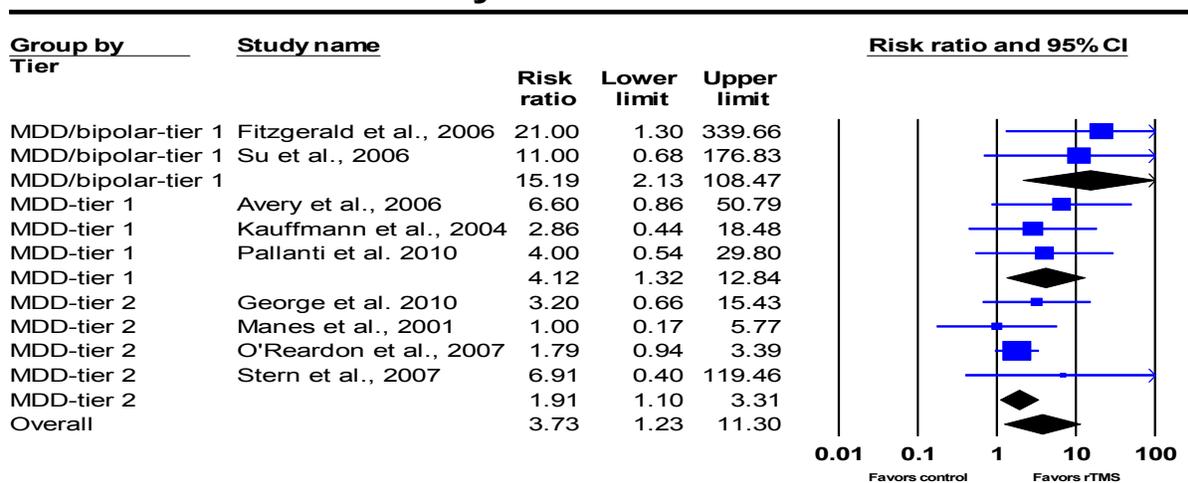
Figure 16. Relative risk meta-analysis of response rates comparing rTMS with sham: Tiers 1 & 2, all populations



Random effects meta-analysis: response; I-squared 0 %

Figure 17. Relative risk meta-analysis of remission rates comparing rTMS with sham: Tiers 1 & 2, all populations

All tiers: any active rTMS vs. control



Random effects meta-analysis: remission; I-squared 0 %

Summary of key Variables

Consideration of all tiers together for the combined MDD and MDD/bipolar mix populations provided results consistent with those from Tier 1 alone but with more conservative point estimates and narrower confidence intervals, suggesting that results from analyses of studies from all tiers reflect what can be expected in TRD (Tier 1) populations. This finding of all tier evidence reflecting what was found with Tier 1 alone held whether the population included was MDD-only or MDD/bipolar mix.

Results from Tiers 1–3 for MDD-only were in the same direction as and of similar magnitude to those for Tier 1–3 MDD/bipolar mix populations. For each outcome, point estimates for the MDD/bipolar mix group were higher with wider confidence intervals, but they were not significantly different from the MDD-only group. When these results were combined, confidence intervals were either equivalent or narrower than when the diagnostic samples were split, suggesting that combining MDD and MDD/bipolar presentations was reasonable.

Only three studies required an antidepressant failure in the current episode;^{73,79,86} there was no clear variation in treatment efficacy between these studies and those not requiring a current episode failure.

At baseline almost all study populations had severe depression,^{18,69-71,74-77,79-81,83,86-88,91} a few had moderate-to-severe depression,^{72,73,84,85,90,92} and in one study population, severity was not reported.⁷⁸ With little variation in depression severity, we were unable to detect any differences by this variable.

In this comparison, 11 studies used an augmentation strategy,^{18,69-75,79-81,90,92} 5 used a switch strategy,^{76,84-88} 3 used a mixed strategy with within-group differences,^{77,78,91} and 1 used a combination strategy with all patients starting a new antidepressant at study entry.⁸³ We were unable to detect clear differences by treatment characteristics (i.e., pharmacotherapy strategy, rTMS frequency, or treatment duration) through qualitative analysis due to other potentially confounding variables resulting from study design or participant characteristics.

Vagus Nerve Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

One trial comparing VNS plus treatment as usual with treatment as usual was identified in Tier 1 (Table 23).⁹⁸

Table 23. Efficacy of VNS versus sham: Tiers 1-3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Rush et al., 2005 ⁹⁸ 10 weeks, m- ITT/per medication protocol Required failure in the current episode Good	VNS (n = 119) 10 weeks of VNS therapy with continued medications. Sham (n = 116) Treatment strategy Augmentation	Diagnosis Bipolar (%) VNS: 11.7 Sham: 9.1 Number of failed antidepressant trials (% ≥ 4): ECT: 46.5% rTMS: 40.0% Baseline Depression HAM-D ₂₄ , mean (SD) VNS: 28.8 (5.3) Sham: 29.7 (5.2)	HAM-D₂₄* % Change, mean (SD) VNS: -16.3 (28.1) Sham: -15.3 (25.5) P = 0.639 *based on VNS n = 112, sham n = 110	HAM-D₂₄* Response, n (%) VNS: 17 (15.2) Sham: 11 (10.0) P = 0.25

HAM-D₂₄ = 24-item Hamilton Depression Scale; mITT = modified intention to treat; P = p-value; SD = standard deviation;
VNS = vagus nerve stimulation

MDD-Only

There were no eligible studies.

MDD/Bipolar

One good 10-week study compared VNS (n = 119 patients) to a control group (n = 116 patients).⁹⁸ This study is summarized in Table 23 with a detailed description provided in the evidence tables (Appendix E). The control group had the surgical procedure to implant the VNS device, but they did not have the device turned on for the sessions. Patients were required to have had an unsatisfactory response to at least two adequate trials of antidepressant medication, but not more than six failures, for the current episode. More than 40 percent of the sample had four or more prior antidepressant treatment failures, indicating a high degree of treatment resistance. The two groups entering into this study were severely depressed, with a mean HAM-D₂₄ score of 28.8 in the VNS group and 29.7 in the control. In a modified ITT analysis that excluded those noncompliant with the medication protocol, the results did not demonstrate a statistically significant difference between the two groups for the primary outcome (HAM-D₂₄). No differences were found in the percentage change in depressive severity (-16.3% for VNS vs. -15.3% for control, $P = 0.639$) or the response rates (15.2% vs. 10.0%, $P = 0.25$). Of note, response rates for a secondary outcome, the 30-item Inventory for Depressive Symptomatology-self report, favored VNS (17.0% vs. 7.3%, $P = 0.032$).

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined Results

Only one study comparing VNS to sham stimulation was identified.⁹⁸ This study is described in the section above.

Psychotherapy Versus Control

Tier 1: Patients With two or More Treatment Failures

There were no eligible studies.

Tier 2: Patients With one or More Failures

MDD-Only

Four Tier 2 studies⁹³⁻⁹⁷ comparing psychotherapy to a control group were identified (Table 24). All indicated improvement with CBT. Only one of these studies received a good-quality rating.^{95,96} Two studies used an augmentation strategy,^{93,95,96} one used an unlimited strategy (patients in both groups may or may not start a new medication),⁹⁷ and the fourth study used a combination strategy with patients in all groups starting a new medication;⁹⁴ the type of treatment strategy produced no clear variation in outcome. The presence of treatment failure in the current episode did not clearly influence outcome. The duration of the trials (all 16–20 weeks) did not vary. Groups in all studies were moderately depressed.

One good 20-week RCT (described in 2 articles) compared 16 sessions of cognitive therapy and clinical management (CM) (n = 80 patients) to CM alone (n = 78 patients).^{95,96} In each case, CM consisted of a visit with a psychiatrist every 4 weeks with minor medication adjustments to

an antidepressant medication regimen allowed. Patients entered the study having residual depressive symptoms ($HAM-D_{17} \geq 8$) despite having received greater than 4 weeks of adequate antidepressant treatment. Depression in both groups was mild (mean $HAM-D_{17}$ for the two groups was 12.1-12.2). In an ITT analysis, there was no difference in the mean decrease in depressive severity (CBT plus CM -3.4 vs. CM alone -2.8, $P = NS$). Remission was defined more stringently as a $HAM-D_{17}$ score ≤ 7 at two consecutive visits 4 weeks apart; using this definition, remission rates were greater for CBT plus CM when compared with CM alone (24% vs. 13%, $P < 0.05$).

One trial compared a 4-month treatment of CBT plus CM ($n = 14$ patients) to CM alone ($n = 11$ patients).⁹⁷ Mean depressive severity at baseline as measured by the BDI was 31.1 for CBT plus CM versus 26.8 for CM, consistent with depression that was moderate to severe. Usual care (UC) in each group resulted in unlimited medication strategy. In an ITT analysis, the CBT plus UC group reduced depressive severity as measured by the BDI by an average of 11.2 points more than the UC group (95% CI, -19.3 to -3.1). Also, the CBT plus UC group had eight patients meeting response criterion, compared to none in the UC group.

Table 24. Efficacy of psychotherapy versus control: Tiers 1-3

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Harley, 2008 ⁹³ 16 weeks, completers analysis Tier 2: Failure not required in current episode Fair	CBT [DBT] (n = 13) 16 sessions of dialectical behavior therapy skill training Control (n = 11) Waitlist Treatment strategy Augmentation Definitions Remission definition: $HAM-D_{17}$ score ≤ 7	Mean number of failed antidepressant trials: CBT: NR Control: NR Baseline Depression $HAM-D_{17}$, mean (SD) CBT: 16.15 (4.47) Control: 18.64 (4.72)	$HAM-D_{17}$* Change, mean (SD) CBT: -5.6 Control: -1.78 $P < 0.05$ * results based on completers (CBT: $n = 10$, Control: $n = 9$)	$HAM-D_{17}$ Remission (%) CBT: 3 (23.1) Control: 0 (0) $P = NR$
Kocsis et al., 2010 ⁹⁴ 12 weeks, completers analysis Tier 2: Required failure in the current episode Fair	CBASP (n=200) 16 to 20 sessions of cognitive behavioral analysis system of psychotherapy BSP (n=195) 16 to 20 sessions of brief supportive psychotherapy No Psychotherapy (n=96) Treatment strategy Combination (all patients received next option on pharamcotherapy algorithm including sertraline, escitalopram, bupropion, venlafaxine, mirtazapine, and lithium) Definitions Remission $HAM-D_{24} < 8$ AND 50% decrease from baseline	Number of failed antidepressant trials: Mean (SD) CBASP: NR BSP: NR No therapy: NR Baseline Depression: $HAM-D_{24}$, mean (SD) CBASP: 19.52 (8.56) BSP: 19.44 (8.31) No therapy: 18.37 (8.00)	$HAM-D_{24}$ Change*, mean (SD) CBASP: -8.23 BSP: -6.67 No therapy: -6.09 $P = NS$ *based on completers CBASP $n = 174$ BSP $n = 168$ No therapy $n = 76$	$HAM-D_{24}$ Remission, n (%) CBASP: 67 (33.5) BSP: 52 (26.7) No therapy: 30 (31.3) $P = NS$

Table 24. Efficacy of psychotherapy versus control: Tiers 1-3 (continued)

Author, Year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Paykel, 1999 ⁹⁵ and Scott, 2000 ⁹⁶ 20 weeks Tier 2: Required failure in the current episode Good	CBT (n = 80) 16 sessions of cognitive therapy plus clinical management CM (n = 78) Clinical management alone Treatment strategy Primarily augmentation with minor medication dose adjustments allowed. Definitions Remission definition: HAM-D ₁₇ score ≤ 7 at 2 consecutive ratings 4 weeks apart	Mean number of failed antidepressant trials: CBT: NR CM: NR Baseline Depression HAM-D ₁₇ , mean (SD) CBT: 12.2 (2.9) CM: 12.1 (2.7)	HAM-D₁₇ Change, mean (SD) CBT: -3.4 CM: -2.8 <i>P</i> = NS	HAM-D₁₇ Remission, n (%) CBT: 19 (24) CM: 10 (13) Hazard Ratio for remission 2.42 (95% CI: 1.08 to 5.45), <i>P</i> = 0.03
Wiles et al., 2008 ⁹⁷ 4 months Tier 2: Required failure in the current episode Fair	CBT plus CM (n = 14) 12-20 sessions of cognitive behavioral therapy and clinical management CM (n = 11) Clinical management, no restrictions Treatment Strategy Unlimited	Mean number of failed antidepressant trials: CBT: NR CM: NR Baseline Depression BDI, mean (SD) CBT: 31.1 (8.5) CM: 26.8 (6.8)	BDI CBT scores decreased by an average of 11.2 points more than CM (95% CI, -19.3 to - 3.1)	BDI Response, n (%) CBT: 8 (57.1) CM: 0 (0.0) <i>P</i> = NR

BDI = Beck Depression Inventory; BSP = Brief Supportive Therapy; CBASP = Cognitive Behavioral Analysis System of Psychotherapy; CBT = cognitive behavioral therapy; CI = confidence interval; CM = clinical management; DBT = Dialectical Behavioral Therapy; HAM-D₁₇ = 17-item Hamilton Depression Scale; n = number; NR = not reported; NS = not significant; *P* = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

One 12-week RCT compared 12 weeks of CBT plus pharmacotherapy (n = 200) with participants receiving pharmacotherapy alone (n = 96).⁹⁴ A third arm assessing Brief Supportive Therapy was included in the study but is not an intervention of interest for this report and is therefore not included in this description. Enrolled patients were required to have an inadequate response (i.e., HAM-D₂₄ ≥ 8) to their medication at baseline. At baseline patients had mild to moderate depression (HAM-D₂₄, mean [SD]: CBT 19.5 [8.6], no CBT (medication only): 18.37 [8.0]). The trial used a combination treatment strategy, starting patients in all groups on a new medication. In a completers analysis, no significant differences were found between groups for decrease in depressive severity or rates of remission.

One 4-month trial compared a distinct form of CBT that involves both group and individual treatments called Dialectical Behavioral Therapy (DBT) (n = 13 patients) to a wait list control (n = 11).⁹³ The two participating groups had moderate depressive severity at study enrollment (HAM-D₁₇ scores averaged 16.15 for DBT group and 18.64 for waitlist control). In a treatment completer analysis at 4 months, the DBT group (n = 10) had a greater decrease in depressive severity than the waitlist group (n = 9) (-5.6 vs. -1.78, *P* < 0.05) and were more likely to achieve remission (23.1% vs. 0%).

We did not quantitatively synthesize these results.

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined Results

Four Tier 2 studies comparing psychotherapy to a control group were identified. One good study reported in two articles^{95,96} and two fair studies^{93,97} supported greater outcomes for patients in psychotherapy compared to a control group. A fourth study, also in a Tier 2 MDD-only population, found no differences between groups for decrease in depressive severity or remission.⁹⁴ Unlike the first three studies,^{93,95-97} the fourth study used a combination strategy and started all patients on a new antidepressant at the beginning.⁹⁴ Two of the studies used augmentation strategies^{93,95,96} and another did not limit the pharmacotherapy strategies of participants.⁹⁷ With only four studies identified for this comparison, it is difficult to determine how study design, participant, or treatment characteristics may have affected treatment efficacy. All four studies fell into Tier 2 and three of the trials⁹⁴⁻⁹⁷ required a failure in the current episode. All patients had MDD. Duration and method of psychotherapeutic interventions were similar across studies.

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Comparisons

In this section, we assess how nonpharmacologic treatments compare with pharmacological treatments in efficacy or effectiveness in treating acute-phase depressive symptoms in patients with TRD; these comparisons can help place nonpharmacologic treatments for TRD within the context of pharmacologic ones. First, we review the literature that directly compares nonpharmacologic and pharmacologic interventions for TRD, using the same approach we did in KQ 1a: categorizing first by intervention comparison, next by tier, and then by MDD versus the MDD/bipolar mix, while considering the role of the same key elements on treatment outcome.

For nonpharmacologic versus pharmacologic comparisons, we identified three studies. One study compared ECT versus pharmacotherapy, and two compared CBT with pharmacotherapy. Only one of these studies involved a TRD (Tier 1) population; enrolling an MDD/bipolar mix sample, it provided data showing that switching to ECT provided a greater decrease in depressive severity than switching to a new pharmacotherapy.⁶⁶

Considering Tier 2 studies added two trials comparing CBT versus pharmacotherapy, both in MDD-only populations.^{101,102} These two studies involved moderately depressed groups and provided data showing that CBT was no different than medication treatments for a variety of treatment strategies.^{101,102} We could not make any conclusions about the impact of tier definition, diagnosis, depressive severity, treatment strategy, treatment characteristics, or treatment failure in the current episode.

For pharmacologic versus pharmacologic treatments, we identified nine trials that used a variety of pharmacologic treatment strategies to treat TRD including switching to a new antidepressant medication¹⁰³⁻¹⁰⁸ and augmenting the current medication.¹⁰⁹⁻¹¹¹ All involved patients who were severely depressed. Response rates for the pharmacologic options did not clearly differ from CBT, but two studies reporting CBT outcomes versus medications did appear to have poorer outcomes than ECT in one study. Finally, mean remission rates for pharmacologic options were similar to those reported in nonpharmacologic studies.

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Overview of Nonpharmacologic Versus Pharmacologic Treatments

Only three studies providing nonpharmacologic versus pharmacologic treatments were available (Table 25).^{66,101,102} Having such a limited database prevented a consideration of the effect on outcome of which tier of evidence was used, whether the population was MDD-only versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, and whether the treatment failure was in the current episode.

Strength of evidence assessments were made for three outcomes: change in depressive severity, response rates, and remission rates. We first will present the strength of evidence for Tier 1 studies alone, and then present strength of evidence for all three tiers considered together.

When possible, within each comparison we report results by treatment strategy since this is a fundamental aspect of the antidepressant therapy.

A single MDD/bipolar mix study⁶⁶ suggested better outcomes for ECT compared with pharmacologic treatment. Two studies found no difference between CBT and pharmacologic options.^{101,102}

Table 25. Number of good- and fair-quality studies by comparison, tier, and diagnostic mix for KQ 1b

Comparison	Tier	MDD-only	MDD and Bipolar Disorder
ECT versus pharmacotherapy	Tier 1 (≥ 2 treatment failures)	0	1
Psychotherapy vs. pharmacotherapy	Tier 2 (≥ 1 treatment failures)	2	0

ECT = electroconvulsive therapy

Strength of Evidence: Tier 1 (TRD)

Only one study providing nonpharmacologic versus pharmacologic treatments was available.⁶⁶ Having such limitations prevented consideration of the effect on outcome whether the population was MDD versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, and whether the treatment failure was in the current episode.

Data were available to allow strength of evidence assessments for two outcomes: change in depressive severity and response rates (Table 26). This single trial provided low strength of evidence that ECT produced better outcomes than medications in a Tier 1 MDD/bipolar mix population; the study did not address remission rates.⁶⁶

Table 26. Strength of Evidence: ECT versus pharmacotherapy

Comparison	Number of Studies; Subjects	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	1; 39	Medium/ High RCT 1 fair	Unknown	Direct	Imprecise	ECT > pharmacotherapy (paroxetine) Low
Response	1; 39	Medium/ High RCT 1 fair	Unknown	Direct	Imprecise	ECT > pharmacotherapy (paroxetine). Low
Remission	0; 0	—	—	—	—	—

ECT = electroconvulsive therapy; RCT = randomized controlled trial

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Key Points of Nonpharmacologic Versus Pharmacologic Treatments

Only four trials provided a direct comparison of nonpharmacologic and pharmacologic treatment for TRD. The limited number of comparisons prevented any firm conclusions regarding the effect on outcome of the tier level of evidence used, whether the population was MDD-only versus MDD/bipolar mix, the degree of depressive severity, the type of treatment strategy, the type of treatment characteristics, or whether the treatment failure was in the current episode.

Electroconvulsive Therapy Versus Pharmacotherapy

One Tier 1 study comparing ECT with pharmacotherapy found a greater change in depressive severity and a higher rate of response for participants in the ECT group.⁶⁶

Cognitive Behavioral Therapy Versus Pharmacotherapy

One Tier 2 study comparing CBT with pharmacotherapy found no differences in change in depressive severity, rate of response, or rate of remission between groups.¹⁰¹ A second study, with a small sample (N = 13), showed a difference in change in depressive severity but did not report the test of statistical significance.¹⁰²

Key Question 1b: Comparisons Involving Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Nonpharmacologic Versus Pharmacologic Treatments

Electroconvulsive Therapy Versus Pharmacotherapy

Tier 1: Patients With two or More Treatment Failures

One study comparing ECT to pharmacotherapy in an MDD/bipolar mix population was identified for Tier 1 (Table 27), finding greater improvement in severity and response for patients receiving ECT versus paroxetine.

MDD-Only

There were no eligible studies.

MDD/Bipolar

One 4-week trial compared outcomes for right-sided unilateral ECT (n = 21 patients) with paroxetine (n = 18 patients, 22 randomized).⁶⁶ All patients discontinued current antidepressant therapy, and patients in the paroxetine group initiated pharmacotherapy. In the ECT group, 9.5 percent of patients (n = 2) had bipolar illness; 16.7 percent (n = 3) had bipolar illness in the medication group. Patients were severely depressed (mean HAM-D₂₁ scores were 31.1 in the ECT group (SD 4.9) and 32.8 (SD 5.4) in the pharmacotherapy group). The ECT group experienced a greater decrease in depressive severity (-18.6 vs. -9.6, *P* = 0.001) and a greater response rate (71.4% vs. 27.8%, *P* = 0.006) than the paroxetine group.

Tier 2: Patients With one or More Failures

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1-3: Combined

Only one study comparing ECT to pharmacotherapy was identified;⁶⁶ this study is described in the section above.

Table 27. Efficacy of ECT versus pharmacotherapy: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Folkerts et al., 1997 ⁶⁶ End of study phase (2-4 weeks), per protocol analysis Tier 1: Did not require failure in the current episode Fair	ECT (n = 21*) Right unilateral, mean txts = 7.2 sessions (2-3 weeks) Pharmacotherapy (n = 18*) Paroxetine 40 mg (max 50 mg/d, mean 44 mg/day) *per protocol Treatment Strategy Switch	Diagnosis Bipolar (%) ECT: 9.5 Pharm: 16.7 Mean number of failed antidepressant trials: ECT: 4.9 Pharm: 4.3 Baseline Depression HAM-D ₂₁ , mean (SD) ECT: 31.1 (4.9) Pharm: 32.6 (5.4)	HAM-D₂₁ Change, mean (SD) ECT: -18.6 Pharm: -9.6 <i>P</i> = 0.001	HAM-D₂₁ Response, n (%) ECT: 15 (71.4) Pharm: 5 (27.8) <i>P</i> = 0.006

ECT = electroconvulsive therapy; ; HAM-D₂₁ = 21-item Hamilton Depression Scale; max = maximum, mg = milligram; mg/d = milligram per day; n = number; *P* = p-value; pharm = pharmacotherapy; SD = standard deviation; txt(s) = treatment(s)

Cognitive Behavioral Therapy Versus Pharmacotherapy

Two Tier 2 studies, both MDD-only, compared psychotherapy versus pharmacotherapy and are described in Table 28. Both studies required an antidepressant failure in the current episode

and used mixed strategies with between-group differences. One study compared augmenting to switching; the second study required that patients randomized to psychotherapy discontinue medications and compared this group to those who continued their antidepressant medications. Studies were similar in duration so no comparison by study duration was made.

Tier 1: Patients With two or More Treatment Failures

There were no eligible studies.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

One study used a randomization strategy that considered patient choice. Sixteen sessions of cognitive therapy were compared to medication treatment as either an augmentation strategy (each was added to citalopram treatment, respectively) or a switch strategy (changed to CT or a different medication treatment).¹⁰¹ Patients entering all arms were of moderate severity (QIDS-SR mean 11 to 12). Using an ITT analysis, no differences in percentage change in depressive symptomatology were found when comparing CT to medication in either the augmentation (-29.5% vs. -28.3%, $P = 0.8302$) or switch (-15.6% vs. -17.2%, $P = 0.9040$) strategy comparisons. For patients who received augmentation to their citalopram, the response rate did not differ for those to whom CT was added ($n = 65$ patients) versus those to whom medication was added ($n = 117$ patients) (35.4% vs. 28.2%, $P = 0.2493$). Similarly, the response rate did not differ between those who switched to CT ($n = 36$ patients) compared to those who switched to a different medication ($n = 86$ patients) (22.2% vs. 26.7%, $P = 0.8390$). As with change in severity and response, no differences between cognitive therapy and pharmacotherapy were found in remission between groups in the augmentation ($P = 0.7803$) or switch group comparisons ($P = 0.9032$).

One small study¹⁰² randomized patients to either switch to 4 months of CBT ($n = 7$) or continue their current medication management ($n = 6$). Enrolled patients had moderate depressive severity (mean HAM-D score at baseline 18.6 for CBT [SD 3.3] and 18.3 [SD 3.9] for medication). A limited treatment completer's analysis of acute phase outcomes at 4 months suggested a greater decrease in severity for the CBT group (-7.6 points [$n = 5$ patients] vs. +1.5 points [$n = 4$ patients], statistical analysis not reported).

MDD/Bipolar

There were no eligible studies.

Tier 3: Patients With Probable TRD

There were no eligible studies.

Tiers 1–3: Combined Results

Only two studies were identified for this comparison.^{101,102} Although one study did not find differences between groups in treatment efficacy (i.e., change in severity, response, and remission),¹⁰¹ the second study showed a difference in change in depressive severity but did not report the results of a test of statistical significance.¹⁰² Both studies were identified in Tier 2, required a failure in the current episode, included only patients with MDD, included samples with moderate depressive severity, and used similar treatment characteristics (i.e., both used

cognitive behavioral therapy and were approximately 4 months in duration). The first study compared treatment arms that augmented with either psychotherapy or a new antidepressant medication and arms that switched to psychotherapy or a new antidepressant.¹⁰¹ The second study compared switching to psychotherapy to continued medication management.¹⁰²

Table 28. Efficacy of psychotherapy versus pharmacotherapy: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
<p>Thase et al., 2007¹⁰¹ 12-14 weeks Required failure in the current episode Fair</p>	<p>Augmentation - Cognitive Therapy (n = 65) Continued citalopram and added CT (16 sessions in 12 weeks) Augmentation - Medication (n = 117) Citalopram plus bupropion SR or buspirone Switch - Cognitive Therapy (n = 36) Switch from citalopram to CT 16 sessions in 12 weeks Switch - Medication (n = 86) Switch from citalopram to sertraline, bupropion SR, or extended-release-XR Treatment strategy Mixed-between group differences Definitions Remission defined as QIDS- SR ≤ 5</p>	<p>Mean number of failed antidepressant trials: Aug CT: NR Aug Med: NR Switch CT: NR Switch Med: NR Baseline Depression QIDS-SR, mean (SD) Aug CT: 11.9 (4.3) Aug Med: 12.0 (4.6) Switch CT: 11.2 (4.3) Switch Med: 12.1 (4.6)</p>	<p>QIDS-SR % Change, mean (SD) Aug CT: -29.8 (40.5) Aug Med: -28.3 (39.6) <i>P</i> = 0.8302 Switch CT: -15.6 (40.7) Switch Med: -17.2 (46.2) <i>P</i> = 0.9040</p>	<p>QIDS-SR Response, n (%) Aug CT: 23 (35.4) Aug Med: 33 (28.2) <i>P</i> = 0.2493 Switch CT: 8 (22.2) Switch Med: 23 (26.7) <i>P</i> = 0.8390 Remission, n (%) Aug CT: 20 (30.8) Aug Med: 39 (33.3) <i>P</i> = 0.7803 Switch CT: 11 (30.6) Switch Med: 23 (26.7) <i>P</i> = 0.9032</p>
<p>Moore et al., 1997¹⁰² 4 months is closest to end of treatment, completers analysis Required failure in the current episode Fair</p>	<p>Cognitive Behavioral Therapy (n = 7) minimum of 4 txts 1st month, 2 txts 2nd month and 1 per month following Continued medication management (n = 6) Continued medication dose within recognized therapeutic threshold Treatment Strategy Mixed- between group differences</p>	<p>Mean number of failed antidepressant trials: CBT: NR Meds: NR Baseline Depression HAM-D₁₇*, mean (SD) CBT: 18.6 (3.3) Meds: 18.3 (3.9) *Completers only (CBT n = 5, Meds n = 4)</p>	<p>HAM-D₁₇ Change*, mean (SD) CBT: -7.6 Meds: +1.5 *Completers only <i>P</i> = NR</p>	<p>HAM-D₁₇ Response: NR at end of txt Remission: NR at end of txt</p>

CT = cognitive therapy; CBT = cognitive behavioral therapy; ; HAM-D₁₇ = 17-item Hamilton Depression Scale;
Meds = continued medication management; n = number; NR = not reported; *P* = p-value; QIDS-SR = Quick Inventory of
Depressive Symptomatology-Self Report; SD = standard deviation; SR = sustained release; txt = treatment; XR = extended
release

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Overview of Pharmacologic Versus Pharmacologic Treatments

All studies reviewed in this section are RCTs that involve Tier 1 TRD (≥ 2 failures of adequate antidepressant trials) and MDD-only patients. This synthesis allows a crude comparison between what one might expect as a “next-step” pharmacologic intervention relative to a next-step nonpharmacologic intervention. Consequently, these studies may provide a reference for the degree of response (or remission) that one could expect from a next-step pharmacologic treatment (relative to a next-step nonpharmacologic treatment).

Some of these studies include a group that did not receive an active primary antidepressant treatment (e.g., olanzapine, which by itself is not used as an antidepressant); these arms will not be considered in the subsequent analyses. We focus instead on the same three outcomes addressed in previous sections—change in depressive severity, response rate, and remission rate. However, we will not formally assess strength of evidence as we did in the prior sections. Rather, we will present the available clinical response data that illustrate what is expected following an active antidepressant treatment. We will consider both responses seen after a change in pharmacologic treatment (either a switch or augmentation) and responses seen after maintenance on the same pharmacologic management without a change in treatment. Finally, also in contrast to our prior sections, we will not consider the role of MDD/bipolar mix or tier definition, as these variables are by definition fixed in this section, but we will attempt to consider the other key elements.

We identified 12 Tier 1 MDD-only studies involving moderately to severely depressed groups that compared pharmacologic treatment as a next treatment step (Table 29).¹⁰³⁻¹¹⁴ We attempted to determine mean effect sizes, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, there were no comparable, common control groups not receiving a mood-related medication to allow such comparisons. Instead, we determined mean average outcomes for pharmacologic treatments. Although we were unable to statistically compare these outcomes, there was broad overlap in their decreases in depressive severity, relative risks of response, and relative risks of remission.

Table 29. Number of good- and fair-quality studies by comparison and definition of treatment resistance (tier) for MDD-only for KQ 1b

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
Pharmacotherapy versus Pharmacotherapy	Tier 1 (≥ 2 treatment failures)	12	NA
Pharmacotherapy versus Pharmacotherapy	Tier 2 (≥ 1 treatment failures)	NA	NA
Pharmacotherapy versus Pharmacotherapy	Tier 3 (probable treatment failure)	NA	NA

MDD = major depressive disorder; NA = not applicable

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Key Points of Direct Comparisons

All studies included in the pharmacologic intervention versus pharmacologic intervention were conducted in patients with MDD-only TRD. We identified 12 studies: 7 studies primarily tested switch strategies^{103-108,112} and 5 assessed augmentation.^{109-111,113,114} Seven of the 12 studies

also included a maintenance arm, allowing further analysis of this strategy as well. To allow comparison to the nonpharmacological interventions, weighted means were calculated for each strategy for the three outcomes of interest.

Regarding changes in depressive severity, mean changes in MADRS scores were similar across the three strategies (switch -11.2 [95% CI, -14.7 to -7.8], augmentation -11.2 [95% CI, -13.7 to -8.8], and maintenance -7.6 [95% CI, -9.2 to -5.2]). Consistent results were seen for response and remission rates (switch 39.8% [95% CI, 30.7-48.9] and 22.3% [95% CI, 16.2-28.4], augmentation 38.1% [95% CI, 31.0-45.3] and 27.2% [95% CI, 20.4-34.0], maintenance 27.3% [95% CI, 19.8-34.8] and 16.8% [95% CI, 13.5-20.2], respectively). These data are limited by the combination of different types of antidepressants and augmenting options included in this analysis.

Only one study did not require a failure in the current episode¹¹⁰ limiting further analysis by this variable. Though some variability in the depressive severity of populations was present, differences by severity were not apparent.

Key Question 1b: Pharmacologic Interventions for Acute Phase Treatment—Detailed Analysis of Direct Comparisons

Tier 1: Patients With two or More Treatment Failures

Twelve studies were identified for this population. Seven of the studies used switch strategies^{103-108,112} and five tested an augmentation strategy.^{109-111,113,114}

Switching Strategies

Seven studies testing a switch strategy were identified and are described in Table 30.^{103-108,112} One study compared the 12-week outcomes for patients who failed venlafaxine treatment and were randomized to one of five groups: a combination of olanzapine (either 6 or 12 mg/day)/fluoxetine (either 25 or 50 mg/day) (n = 243 patients, pooled from 4 groups), olanzapine alone (either 6 or 12 mg/day) (n = 62 patients), fluoxetine alone (either 25 or 50 mg/day) (n = 60 patients), a “pseudo placebo” low-dose combination of olanzapine (1mg/day) and fluoxetine (5 mg/day) (n = 59 patients), or continuing with venlafaxine alone (75-375 mg/day) (n = 59 patients).¹⁰³ Only one treatment failure was required in the current episode (failure to respond to venlafaxine). Baseline depressive severity for the overall sample was in the moderate-to-severe range (MADRS 30.0). An ITT analysis favored the olanzapine/fluoxetine combination versus fluoxetine alone in all depression outcome comparisons, but showed no difference between any of the other groups. The combination was better than fluoxetine alone for greater change in depressive severity (-14.06 vs. -7.71, $P < 0.001$; other severity changes ranged from -11.7 to -13.73), greater response rate (43.3% vs. 25.4%, $P = 0.017$; other response rates ranged from 33.9% to 50.0%) and greater remission rate (29.9% vs. 13.8%, $P = 0.013$; other remission rates ranged from 17.9% to 22.4%).

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Corya et al., 2006 ¹⁰³ 12 weeks Required failure in the current episode Fair	<p>OLA-FLU (n = 243) Combined 4 groups OLA (n = 62) 6 or 12mg/d FLU (n = 60) 25 or 50 mg/d VEN (n = 59) 75-375mg/d LD OLA plus FLU (n = 59) 1mg/d OLA, 5mg FLU Treatment strategy OLA-FLU: Switch OLA: Not of interest FLU: Switch VEN: Maintenance LD OLA-FLU: Switch Definitions Remission defined as MADRS ≤ 8 at two consecutive visits</p>	<p>Baseline Depression MADRS, mean (SD) Overall: 30.0 (6.8)</p>	<p>MADRS Change, mean (SD) OLA-FLU: - 14.06 (0.59) OLA: -7.71 (1.17) FLU: -11.70 (1.14) VEN: -13.73 (1.16) LD OLA-FLU: - 11.97 (1.13) OLA-FLU versusOLA <i>P</i> < 0.001 all others NS</p>	<p>MADRS Response, n (%) OLA-FLU: 100 (43.3) OLA: 15 (25.4) FLU: 19 (33.9) VEN: 29 (50.0) LD OLA-FLU: 20 (36.4) OLA-FLU versus OLA, <i>P</i> = 0.017 All others NS Remission, n (%) OLA-FLU: 69 (29.9) OLA: 8 (13.8) FLU: 10 (17.9) VEN: 13 (22.4) LD OLA-FLU: 11 (20.0) OLA-FLU versus OLA, <i>P</i> = 0.013. All others NS</p>
Fang et al., 2010 ¹¹² 8 weeks, ITT Required failure in the current episode Fair	<p>MIR (n = 55) 45mg/day PAR (n = 45) 20 mg/day VEN (n = 50) 225mg/day Treatment strategy MIR: Switch PAR: Switch VEN: Switch Definitions Remission: HAM-D₁₇ ≤ 7</p>	<p>Baseline Depression HAM-D₁₇, mean (SD) Overall: 24.6 (5.8)</p>	<p>HAM-D₁₇ Change, mean (SD) NR</p>	<p>HAM-D₁₇ Response, n (%) MIR: 32 (58.2) PAR: 30 (66.7) VEN: 32 (64.0) <i>P</i> = 0.664 Remission, n (%) MIR: 20 (36.4) PAR: 21 (46.7) VEN: 21 (42.0) <i>P</i> = 0.578</p>
Fava et al., 2006 ¹⁰⁴ 14 weeks Required failure in the current episode Good	<p>MIR (n = 114) Up to 60 mg/d NOR, (n = 121) Up to 200 mg/d Treatment strategy MIR: Switch NOR: Switch Definitions Remission defined as HAM- D₁₇ ≤ 7</p>	<p>Baseline Depression HAM-D₁₇, mean (SD) MIR: 19.8 (7.0) NOR: 18.6 (5.9)</p>	<p>HAM-D₁₇ Change: NR</p>	<p>HAM-D₁₇ Remission, n MIR: 14 (12.3) NOR: 24 (19.8) <i>P</i> = 0.27</p>
Mazeh et al., 2007 ¹⁰⁵ 6 weeks* only in the elderly Required failure in the current episode Fair	<p>PAR (n = 15) 10-60 mg/d, mean = 26mg/d VEN (n = 15) 75-300 mg/d, mean = 165mg/d Treatment strategy PAR: Switch VEN: Switch Definitions Remission defined as HAM- D₂₁ ≤ 7</p>	<p>Baseline Depression HAM-D₂₁, mean (SD) PAR: 30.1 (7.9) VEN: 26.3 (5.9)</p>	<p>HAM-D₂₁ Change, mean (SD) PAR: -12.5 VEN: -19.1 <i>P</i> < 0.0003</p>	<p>HAM-D₂₁ Response, n (%) PAR: 8 (53) VEN: 12 (80) <i>P</i> = NR Remission, n (%) PAR: 5 (33) VEN: 9 (60) <i>P</i> = NR</p>

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1 (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
<p>McGrath et al., 2006¹⁰⁶ 12 weeks Required failure in the current episode Good</p>	<p>TRAN (n = 58) 10 mg/d for 2wk, weekly increases of 10 mg/d until intolerance or 60 mg/d maximum VEN ER plus MIR (n = 51) VEN - 37.5mg/d week 1, 75mg/d week 2, 150 mg/day weeks 3-5, 225 mg/d weeks 6-8, 300 mg/d thereafter MIR—15mg/d weeks 1-2, 30 mg/d next 8 weeks, 45mg/d thereafter Treatment strategy TRAN: Switch VEN-MIR: Switch Definitions Remission defined as HAM-D₂₁ ≤ 7</p>	<p>Baseline Depression HAM-D₁₇, mean (SD) TRAN: 19.6 (7.6) VEN-MIR: 19.7 (5.5)</p>	<p>HAM-D₁₇ Change: NR</p>	<p>HAM-D₁₇ Remission, n (%) TRAN: 4 (6.9) VEN-MIR: 7 (13.7) P = NS</p>
<p>Poirier and Boyer, 1999¹⁰⁷ 4 weeks Required failure in the current episode Fair</p>	<p>VEN (n = 61) 37.5mg/twice day, increased to 200 - 300 mg/d PAR (n = 62) initiated at 20 mg/day and increased to 30—40 mg/d Treatment strategy VEN: Switch PAR: Switch Definitions Remission defined as HAM-D₁₇ < 10</p>	<p>Baseline Depression HAM-D₁₇, mean (SD) VEN: 24.6 (3.9) PAR: 24.5 (4.1)</p>	<p>HAM-D₁₇ Change*, mean (SD) VEN: -11.1 (8.5) PAR: -10.2 (6.8) P = 0.55 ITT, P = 0.70 *N observed (VEN: 52, PAR: 55)</p>	<p>HAM-D₁₇ Response, n VEN: 27 (44.3) PAR: 18 (29.0) ITT, P = 0.07 Remission, n VEN: 22 (36.1) PAR: 11 (17.7) ITT, P = 0.02</p>

Table 30. Efficacy of pharmacotherapy versus pharmacotherapy, switching strategies: Tier 1 (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Shelton et al., 2005 ¹⁰⁸ 8 weeks Did not require failure in the current episode Good	<p>OLA-FLU combination (n = 146) 6 mg/d OLA plus 25mg/d FLU or 12mg/d OLA plus 50 mg/d FLU</p> <p>OLA (n = 144) 6-12mg/d</p> <p>FLU (n = 142) 25 to 50 mg/d</p> <p>NOR, (n = 68) Max dose 175mg/d</p> <p>Treatment strategy OLA+FLU: Switch OLA: Not of interest FLU: Switch NOR: Maintenance</p>	<p>Baseline Depression MADRS, mean (SD) OLA-FLU: 28.5 (7.5) OLA: 28.4 (7.3) FLU: 28.4 (7.3) NOR: 28.8 (6.5)</p>	<p>MADRS Change, mean (SE) OLA-FLU: -8.71 (0.70) OLA: -6.95 (0.71) FLU: -8.51 (0.70) NOR: -7.46 (0.98) FLU versus OLA-FLU, $P = 0.841$ OLA versus OLA-FLU, $P = 0.77$</p>	<p>MADRS Response, n (%) OLA-FLU: 40 (27.5) OLA: 27 (19.3) FLU: 41 (28.9) NOR: 20 (30.3) $P = 0.18$ Remission, n (%) OLA-FLU: 24 (16.9) OLA: 18 (12.9) FLU: 18 (13.3) NOR: 12 (18.2) $P = 0.62$</p>

FLU = fluoxetine; HAM-D₁₇ = 17-item Hamilton Depression Scale; HAM-D₂₁ = 21-item Hamilton Depression Scale; ER = extended release; ITT = intention to treat; LD = low-dose; OLA = olanzapine; MADRS = Montgomery-Asberg Depression Rating Scale; mg/d = milligrams per day; MIR = mirtazapine; n = number; NOR = nortriptyline; NR = not reported; NS = not significant; OLA-FLU = olanzapine/fluoxetine; PAR = paroxetine; SD = standard deviation; TRAN = tranlycypromine; VEN = venlafaxine; wk = week

A fair 8-week study compared switching to one of three antidepressants: mirtazapine (n = 55), paroxetine (n = 55), or venlafaxine (n = 50). Patients were required to have at least one treatment failure in the current episode and were severely depressed at baseline (mean HAM-D₁₇ 24.6). In an ITT analysis, response and remission rates did not differ between groups.

A good-quality study lasting 12–14 weeks compared switching to mirtazapine (up to 60 mg/day; n = 114 patients) or nortriptyline (up to 200 mg/day; n = 121 patients) in a group of patients who had two adequate antidepressant treatment failures in the current episode.¹⁰⁴ Enrolled patients were severely depressed at baseline (mean HAM-D₁₇ 18-20). Response rates as measured by the QIDS-SR did not differ significantly (13.4% for mirtazapine vs. 16.5% for nortriptyline). Similarly, remission rates did not differ significantly between the mirtazapine and nortriptyline groups (12.3% vs. 19.8%, $P = 0.27$).

A 6-week study compared outcomes for patients 65 years and older who were randomized to receive venlafaxine (75 mg to 300 mg/day, mean daily dose 165 mg/day; n = 15 patients) or paroxetine (10-60 mg/day, mean 26 mg/day; n = 15 patients).¹⁰⁵ Patients had two failures of adequate trials during the current episode and were severely depressed at study entry (mean HAM-D₂₁ 26-30). In an ITT analysis, the decrease in depressive severity after 6 weeks was greater for venlafaxine than paroxetine (-19.1 vs. -12.5, $P < 0.0003$). Differences between response rates (80% vs. 53%, $P = \text{NR}$) and remission rates (60% vs. 33%) in this small sample was less clear.

One study compared 12-week outcomes for patients with treatment failure following three adequate antidepressant treatments in the current episode. Patients were randomized to

tranylcypromine (10 mg to 60 mg/day) (n = 58 patients) or a combination of venlafaxine ER (37.5 mg to 300 mg/day) plus mirtazapine (15 to 45 mg/day) (n = 51 patients).¹⁰⁶ Patients were severely depressed at study entry (mean HAM-D₁₇ 19-20). Outcomes tended to favor the venlafaxine/mirtazapine combination, but not to a statistically significant degree. In an ITT analysis, response rates (as measured by the QIDS-SR) did not significantly differ (12.1% with tranylcypromine vs. 23.5% with venlafaxine plus mirtazapine), nor did the remission rates measured by HAM-D₁₇ (6.9% vs. 13.7%).

Another venlafaxine/paroxetine study compared 200–300 mg/day of venlafaxine (n = 61 patients) to 30–40 mg/day of paroxetine (n = 62 patients) for 4 weeks.¹⁰⁵ Patients had treatment failure following two adequate treatments other than venlafaxine or paroxetine in the current episode. Enrolled patients were severely depressed at study entry (mean HAM-D₂₄₋₂₅). The authors conducted an ITT analysis. The change in depressive severity did not differ between the two groups. However, the response rate tended to favor venlafaxine (44.3% vs. 29.0%, $p = 0.07$), and the remission rate supported venlafaxine over paroxetine (36.1% vs. 17.7%, $P = 0.02$).

Another olanzapine/fluoxetine switch study compared the 8-week outcomes for four groups following nortriptyline treatment failure: a combination of olanzapine (6 mg/day or 12 mg/day)/fluoxetine (25 mg/day or 50 mg/day) (n = 146 patients), olanzapine alone (6–12 mg/day) (n = 144 patients), fluoxetine alone (25–50 mg/day) (n = 142 patients), and continuing on nortriptyline alone (50–175 mg/day) (n = 68 patients).¹⁰⁸ Only one treatment failure was required to be in the current episode (failure to respond to nortriptyline). Baseline depressive severity for each group averaged between 28 and 29 on the MADRS, consistent with moderate-to-severe depressive severity. A mixed-effects model repeated-measures regression showed no differences between the four groups in decrease in depressive severity (-8.71, -6.95, -8.51, and -7.46, respectively, $P = \text{NS}$), response rates (27.5%, 19.3%, 28.9%, and 30.3%, respectively, $P = 0.18$), or remission rates (16.9%, 12.9%, 13.3%, 18.2%, respectively, $P = 0.62$).

Augmenting Strategies

Five studies tested augmenting strategies and are described in Table 31.^{109-111,113,114} Two fair studies assessing the efficacy of augmenting with aripiprazole were identified.^{113,114} Patients in both studies had a failed antidepressant trial in the current episode with 2 or more failures overall and were moderately depressed at baseline (mean MADRS [SD]: study 1¹¹³: ARI 26.0 [6.1] placebo 25.9 [6.5]; study 2¹¹⁴: ARI 26.6 [5.8] placebo 27.1 [5.8]). In modified ITT analyses, both studies found significantly greater outcomes for ARI when compared with placebo across all three outcomes of interest.^{113,114}

Table 31. Efficacy of pharmacotherapy versus control, augmenting strategies

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Berman et al., 2007 ¹¹³ 6 weeks, mITT Required failure in the current episode Fair	ARI (n = 184) Placebo (n = 178) Treatment strategy ARI: Augmentation Placebo: Maintenance All patients receiving ESC, FLU, PAR, SER, VEN at maximum tolerated dose; ARI (2-20 mg/day) Definitions Remission defined as MADRS < 10 and ≥ 50% decrease in score	Baseline Depression MADRS, mean (SD) ARI: 26.0 (6.1) Placebo: 25.9 (6.5)	MADRS Change*, mean (SD) ARI: -8.8 Placebo: -5.8 $P < 0.001$ *mITT ARI N = 181 Placebo: 172	MADRS Response, n (%) ARI: 61 (33.2) Placebo: 41 (23.0) $* P \leq 0.05$ Remission, n (%) ARI: 47 (25.5) Placebo: 27 (15.2) $* P \leq 0.01$
Berman et al., 2009 ¹¹⁴ 6 weeks, mITT Required failure in the current episode Fair	ARI (n = 177) Placebo (n = 172) Same antidepressant medications as above Treatment strategy ARI: Augmentation Placebo: Maintenance All patients receiving ESC, FLU, PAR, SER, VEN at maximum tolerated dose; ARI (2-20 mg/day) Definitions Remission defined as MADRS < 10 and ≥ 50% decrease in score	Baseline Depression MADRS, mean (SD) ARI: 26.6 (5.8) Placebo: 27.1 (5.8)	MADRS Change*, mean (SD) ARI: -10.1 Placebo: -6.4 $P < 0.001$ *mITT ARI: N = 174 Placebo: N = 169	MADRS Response, n (%) ARI: 81 (45.8) Placebo: 45 (26.2) $* P \leq 0.001$ Remission, n ARI: 64 (36.2) Placebo: 32 (18.6) $*P \leq 0.001$
Nierenberg et al., 2003 ¹⁰⁹ 6 weeks Required failure in the current episode Fair	LITH Augmentation (n = 18) Dosing strategy NR Placebo (n = 17) All patients continued nortriptyline Treatment strategy LITH: Augmentation Placebo: Maintain	Baseline Depression HAM-D ₂₁ , mean (SD) LITH: 18.8 Placebo: 19.8	HAM-D₂₁ Change, mean (SD) LITH: -2.9 Placebo: -3.6 $P = \text{NR}$	HAM-D₂₁ Response, n (%) LITH: 2 (11.1) Placebo: 3 (17.6) $P = \text{NS}$
Shelton et al., 2001 ¹¹⁰ 8 weeks Required failure in the current episode Fair	OLA+ Placebo (n = 8) 5-20 mg/d FLU+ Placebo (n = 10) 20-60 mg/d OLA+FLU (n = 10) same dose as above Treatment strategy OLA+PLA: Not of interest FLU+PLA: Maintain OLA: Augmentation	Baseline Depression MADRS: NR	MADRS Change, mean (SD) OLA+ Placebo: -2.8 FLU+ Placebo: -1.2 OLA+FLU: -13.6	MADRS Response, n (%) OLA+ Placebo: 0 (0) FLU+ Placebo: 1 (10) OLA+FLU: 6 (60) OLA-FLU versus OLA+ Placebo, $P = 0.03$ OLA+FLU versus FLU+ Placebo, $P = 0.11$

Table 31. Efficacy of pharmacotherapy versus control, augmenting strategies (continued)

Author, year Endpoint Current Episode Failure Requirement Quality	Intervention and Sample Size Study Details	Population Characteristics	Change in Depressive Symptoms	Response Remission
Thase et al., 2007 ¹¹¹ 8 weeks Required failure in the current episode Fair	<p>OLA+FLU (n = 200) OLA 6, 12, or 18 mg/day plus 50 mg/day FLU</p> <p>OLA (n = 206) 6, 12, or 18 mg/day</p> <p>FLU (n = 200) 50 mg/day</p> <p>Treatment strategy OLA-FLU: Augmentation OLA: Not of interest (Switch) FLU: Maintain</p>	<p>Baseline Depression MADRS, mean (SD) OLA+FLU: 30.0 (6.7) OLA: 29.9 (6.4) FLU: 29.9 (6.7)</p>	<p>MADRS Change, mean (SD) OLA+FLU: -12.6 (10.3) OLA: -9.2 (9.7) FLU: -8.9 (9.0) OLA+FLU versus OLA, <i>P</i> < 0.001 OLA+FLU versus FLU, <i>P</i> < 0.001</p>	<p>MADRS Response, n (%) OLA+FLU: 80 (40.4) OLA: 60 (29.6) FLU: 51 (25.9) OLA+FLU versus FLU, <i>P</i> = 0.028 OLA+FLU versus OLA, <i>P</i> = 0.003 Remission, n (%) OLA+FLU: 54 (27.3) OLA: 34 (16.7) FLU: 29 (14.7) OLA+FLU versus OLA, <i>P</i> = 0.012 OLA+FLU versus FLU, <i>P</i> = 0.003</p>

ARI = aripiprazole; ESC = escitalopram; FLU = fluoxetine; HAM-D₂₁ = 21-item Hamilton Depression Scale; LITH = lithium, n = number; MADRS = Montgomery-Asberg Depression Rating Scale; mg/d = milligrams per day; mITT = modified intention to treat; NR = not reported; NS = not significant; OLA = olanzapine; OLA-FLU = olanzapine+fluoxetine; OLA+PLA = olanzapine plus placebo; PAR = paroxetine; SD = standard deviation; SER = sertraline; VEN = venlafaxine

Another study compared outcomes at 6 weeks for patients who had not responded to a 7-week nortriptyline trial and were assigned to augment nortriptyline with either lithium (dose not clarified; n = 18 patients) or placebo (n = 17 patients).¹⁰⁹ Prior to their nortriptyline trial, they had at least one but no more than five treatment failures following antidepressant medication treatment during the current episode. Patients were moderately depressed at study entry (mean HAM-D₁₇₋₁₈). In an ITT analysis, change in depressive severity did not differ between groups (-2.9 for lithium augmentation vs. -3.6 for placebo, *P* = 0.72). Similarly, response rates did not differ significantly for lithium augmentation versus placebo augmentation (11.1% vs. 17.6%, *P* = NS).

A third study compared outcomes at 8 weeks for patients who had two treatment failures to different classes of antidepressants and had an additional failed trial of fluoxetine in the current episode. These patients were assigned to either switch to olanzapine (5 to 20 mg/day; n = 8 patients), add olanzapine (5 to 20 mg/day) to fluoxetine (20 to 60 mg/day) (n = 10 patients) or continue with fluoxetine (50 mg/day) with placebo added (n = 10 patients).¹¹⁰ Baseline mean depressive severity was not reported. The olanzapine/fluoxetine augmentation group had a greater decrease in HAM-D₂₁ items severity than either the olanzapine switch group (-11.7 vs. -5.9, *P* = 0.03) or the fluoxetine continuation group (-11.7 vs. -3.8, *P* = 0.07). The olanzapine/fluoxetine augmentation group also had a greater response rate than the olanzapine switch group (60% vs. 0%, *P* = 0.03) and a trend towards greater response than the fluoxetine continuation group (60% vs. 10%, *P* = 0.11).

Lastly, a study that consisted of two parallel, concurrent trials compared the 8-week outcomes of an olanzapine/fluoxetine combination (6, 12, or 18 mg olanzapine plus 50 mg/day of fluoxetine; n = 200 patients), olanzapine (6, 12, or 18 mg/day; n = 199 patients), or fluoxetine

(50 mg/day; n = 206 patients).¹¹¹ The pooled analyses are reported here. Treatment failure was in the current episode. Patients entering the study were moderately to severely depressed (MADRS score of approximately 30). ITT analyses at study end favored the combination treatment relative to the other two groups in each instance. The combination produced greater differences between groups in the decrease in depressive severity (-10.8 vs. -10.1 in olanzapine only, and vs. -9.4 in fluoxetine only, $P < 0.001$ in each instance); a greater response rate (40.4% vs. 25.9%, [$P = 0.003$] and vs. 29.6% [$P = 0.028$], respectively); and a greater remission rate (27.3% vs. 14.7% [$P = 0.003$] and versus 16.7% [$P = 0.012$], respectively).

Synthesis of MDD Outcomes (Tier 1)

To provide information reporting average outcomes in pharmacologic trials of TRD, we calculated weighted means for the change in depressive severity, response rate, and remission rate (Table 32).

Table 32. Mean clinical outcomes for TRD (Tier 1) patients in pharmacologic studies

Clinical Outcome	Switching	Augmentation	Maintenance
Mean change HAM-D	-10.6 (-16.4 to -4.9)	No data	No data
Mean change MADRS	-11.2 (-14.7 to -7.8)	-11.2 (-13.7 to -8.8)	-7.6 (-9.2 to -5.2)
Mean response rates (HAM-D and MADRS)	39.8% (30.7 to 48.9)	38.1% (31.0 to 45.3)	27.3% (19.8 to 34.8)
Mean remission rates (HAM-D and MADRS)	22.3% (16.2 to 28.4)	27.2% (20.4 to 34.0)	16.8% (13.5 to 20.2)

HAM-D = Hamilton Rating Scale for Depression; MADRS = Montgomery-Asberg Depression Rating Scale
 Note: Numbers in parenthesis indicate the 95 percent confidence interval

We quantitatively synthesized weighted means of the changes in depressive severity for studies involving the two interviewer-administered instruments, the HAM-D and MADRS. For patients switched to a new medication, the mean average change in HAM-D was -10.6 points, and the mean average change in studies using the MADRS was -11.2. For patients receiving medication augmentation, the mean change in depressive severity was -11.2 on the MADRS. We also identified seven measures of depressive severity change in patients who continued on their same medication without a change in treatment. Those measured by MADRS showed a mean change of -7.6, with confidence intervals overlapping with switching and augmentation results.

For changes in response rates, results varied greatly, with response rates ranging from 12.1 to 80 percent. The two highest response rates were from a study restricted to an elderly population,¹⁰⁵ a sample distinct from the others. A weighted mean response rate for switch strategies was 39.8 percent. Considering augmentation strategies provided seven more measures, ranging from 11.1 percent to 45.8 percent. A quantitative synthesis of these rates suggests an average response rate of 38.1 percent for TRD patients following an augmentation next-step pharmacologic treatment. For those who maintained on their pharmacologic treatment, we identified five measures of response rates, which ranged from 10 percent to 50 percent. The weighted mean average response rate for maintenance treatment was 27.3 percent.

Finally, for changes in remission rates, we identified measures involving switch strategies that were not restricted to the elderly population. These remission rates ranged from 6.9 percent to 46.7 percent, with a weighted mean average remission rate of 22.3 percent for TRD patients following a switch to a next-step pharmacologic treatment. Five studies with augmentation arms provided five augmentation measures of remission rates, ranging from 15.2 percent to 29.9 percent, with a weighted mean average remission rate of 27.2 percent. For those who maintained

on their pharmacologic treatment, measures of remission showed rates varying from 14.7 percent to 22.4 percent, with a weighted mean average remission rate of 16.8 percent.

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Overview

As with KQ 1, KQ 2 addressed direct or indirect comparisons of the four nonpharmacological interventions (ECT, rTMS, VNS, and either CBT or IPT). Unlike KQ 1, however, we did not include studies that compared pharmacologic interventions. In the detailed analysis section below, first we present the studies by comparison, then by tier, and then by whether the population involves MDD-only patients or an MDD/bipolar mix. Information is presented for the three tiers used in KQ 1 (Tier 1, two or more treatment failures; Tier 2, one or more treatment failures, but not including the studies in Tier 1; and Tier 3, “probable” treatment resistance). Again, only studies with quality ratings of good or fair are featured.

Table 33. Number of studies included by comparison and definition of treatment resistance (tier) for KQ 2

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	2	1
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2 additional	1 additional
rTMS vs. sham	Tier 3: Probable	0	1 additional
ECT vs. rTMS	Tier 3: Probable	1 additional	2 additional
CBT vs. usual care	Tier 3: Probable	1 additional	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; vs. = versus.

We identified a total of 11 studies addressing maintenance of remission

using nonpharmacologic interventions (Table 33). Two Tier 1 studies, reported in three articles, compared rTMS versus sham in an MDD-only population, with both indicating that rTMS was superior to sham in preventing relapse.^{69,77,99} However, these trials included very few patients in the relapse prevention phase. A third Tier 1 study compared rTMS with sham in an MDD/bipolar mix population. Differences between rTMS and sham were not statistically significant at 1- and 3-months followup.⁸²

Tier 2 evidence added three trials comparing rTMS versus sham. Two of these trials involved MDD-only patients (five articles).^{86,87,115,116} One study involved an MDD/bipolar mix population.⁸⁸ All three trials supported benefit of rTMS over sham in maintaining remission.

Tier 3 evidence added five studies. One study compared rTMS versus sham in an MDD/bipolar mix population, finding benefit again for rTMS over sham.⁹⁰ Three studies provided the only head-to-head comparison available, comparing ECT versus rTMS, one in an MDD-only population that was reported in two articles^{117,118} and two in an MDD/bipolar mix population that was reported in four articles.⁶⁰⁻⁶³ All studies indicated no difference in maintaining remission at 7 weeks to 6 months followup.

Most studies either allowed patients to continue antidepressants throughout the trial or required that they be given an antidepressant following the active nonpharmacological treatment. The duration of followup for assessing maintenance of remission ranged from 2 weeks to nearly 1 year. The method for assessing maintenance of remission varied among trials. Some trials followed (or randomized) only patients who had achieved a response or remission during active treatment and then measured relapse during a post-treatment period. Other trials followed all

randomized participants during a post-treatment period regardless of response or remission with initial treatment. These trials generally reported the number of patients in remission at the end of treatment and at the end of followup, which provides an indirect measure of maintenance of remission.

Strength of Evidence: Tier 1

There were no Tier 1 direct (head-to-head) comparisons available. The single comparison involving a Tier 1 TRD population was rTMS versus sham; three studies provided insufficient evidence to draw a conclusion (Table 34). Studies found that relapse rates do not differ significantly between rTMS and sham, however, too few patients were followed during the continuation phases of these two studies and patients in the third received a co-intervention, providing insufficient evidence to allow for a conclusion.

Table 34. Strength of Evidence: maintenance of remission of rTMS versus sham – Tier 1

Comparison	Number of studies; subjects*	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
rTMS vs. sham	3; 46	High 3 RCTs Fair	Inconsistent	Indirect	Imprecise	No significant differences in maintenance of remission Insufficient

* Number of subjects reflects only those followed past acute treatment

RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease: Key Points

Only limited evidence addressed maintenance of remission among MDD patients. These included the following interventions: ECT (2 studies), rTMS (10 studies, including ECT in three head-to-head trials), and CBT (1 study). No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT in patients in a TRD (Tier 1) population. No evidence was identified for VNS. The only evidence for TRD (Tier 1) compared rTMS versus sham.

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

No TRD (Tier 1) data were available for this comparison, but three trials provided direct Tier 3 evidence. One trial in an MDD-only population, reported in two articles, found no statistically significant differences in relapse rates at 3 months and 6 months after treatment ended.^{117,118} A second trial in an MDD/bipolar mix population, reported in three articles, provided similar results indicating no statistically significant differences in relapse rates between ECT and rTMS.⁶¹⁻⁶³ A third trial in an MDD/bipolar mix population reported no statistically significant differences in response and remission rates during a 4-week observation following 3 weeks of acute treatment.⁶⁰ However, results of this trial may be confounded by a large number of rTMS patients switching to ECT.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Two Tier 1 MDD-only studies found no statistically significant differences in relapse rates between rTMS and sham at 20 weeks⁶⁹ and 6 months.^{77,99} A third Tier 1 study, involving an MDD/bipolar mix population, found no statistically significant differences in mean HAM-D scores during acute treatment at 3-month followup.⁸² These three studies provided insufficient evidence to draw a conclusion. Studies found that relapse rates do not differ significantly between rTMS and sham, however, too few patients were followed during the continuation phases of two of these studies and patients in the third received a co-intervention, providing insufficient evidence to allow for a conclusion.

Three Tier 2 studies provided data supporting the benefit for rTMS versus sham in maintaining remission. One MDD-only study found greater improvement in symptoms for rTMS patients than for the control patients at 2 weeks post-treatment.⁸⁶ Only the high-frequency rTMS delivered to the left dorsolateral prefrontal cortex and the low-frequency rTMS delivered to the right left dorsolateral prefrontal cortex were more effective than the sham intervention. A second study, also in an MDD-only population, found a trend towards lower relapse rates for rTMS compared with sham, but statistically significant differences were not reported.^{87,115,116,119} One study involving an MDD/bipolar mix population reported that one patient who responded after rTMS maintained response at 2-month followup.⁸⁸

One Tier 3 study, involving an MDD/bipolar mix population, showed benefit for rTMS versus sham for 3 weeks after treatment ended, but the benefit had disappeared at 3-month followup.⁹⁰

Cognitive Behavioral Therapy Versus Usual Care

No TRD (Tier 1) evidence was available for this comparison. One relatively large study (150 patients) reported in four articles involved a Tier 3, MDD-only population; it supported the benefit of CBT versus usual care in maintaining remission.^{95,96,120,121} The initial study compared 20 weeks of CBT with usual care (clinical management involving psychiatrist visits and antidepressant medications) and measured remission rates over a total of 68 weeks. Patients treated with CBT had a lower risk of relapse than sham-treated patients (hazard ratio 0.54; 95% CI, 0.32-0.93; $P = 0.02$). Followup of this population for 6 years after randomization showed small differences in recurrence rates for up to 3.5 years, although actuarial recurrence rates were only statistically significantly different through 20 weeks after randomization.

**Key Question 2: Efficacy or Effectiveness for Maintaining Remission or Treating Patients With Unresponsive or Recurrent Disease:
Detailed Analysis**

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD/bipolar mix population.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with ECT versus rTMS therapy in an MDD/bipolar mix population.

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

In the RCT of ECT versus rTMS,^{117,118} 43 participants entered treatment, but only 41 continued in the 6-month followup to assess relapse rates (Table 35). In 20 participants, ECT was delivered according to a protocol with intensity 2.5 times the threshold energy and charge titrated up every second or third treatment to maintain a seizure length of 25 seconds or longer. Twenty-one participants received 20 sessions of high frequency at 90 percent motor threshold and 1,200 pulses per second. Prior to beginning treatment, the mean HAM-D₁₇ scores (standard deviation) for patients were 28.4 (9.3) in the ECT group and 25.8 (6.1) in the rTMS group. At the beginning of followup (i.e., end of treatment), mean HAM-D₁₇ scores were 7.9 (4.5) in the ECT group and 7.8 (3.7) in the rTMS group. These scores remained relatively stable at 3 and 6 months after treatment ended. At 3 months, 2 of 20 (10%) ECT-treated participants and 1 of 21 (5%) rTMS-treated participants relapsed. At 6 months, the figures were 4 of 20 (20%) and 4 of 21 (19%), respectively. Relapse rates were not statistically significantly different between these groups.

Table 35. Maintenance of remission of ECT versus rTMS: Tier 3, MDD

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Dannon et al., 2002; ¹¹⁷ extension of Grunhaus et al., 2000 ¹¹⁸ RCT Fair	<p>ECT plus antidepressant post-ECT (n = 20) 35% bilateral, mean sessions = 10.25 (3.1)</p> <p>rTMS plus antidepressant post-rTMS (n = 21) High frequency, 20 sessions</p> <p>Definitions Response: HAM-D₁₇ reduction ≥ 50% and final GAS < 60 Relapse: return of depressive symptoms with HAM-D₁₇ ≥ 16 Measured at end of treatment (response) and 3 and 6 months post-treatment (relapse)</p>	<p>HAM-D₁₇ End of treatment (baseline), mean (SD) ECT: 7.9 (4.5) rTMS: 7.8 (3.7) <i>P</i> = NS</p> <p>3-month post-treatment, mean (SD) ECT: 7.7 (5.0) rTMS: 6.4 (4.9) <i>P</i> = NS</p> <p>6-month post-treatment, mean (SD) ECT: 8.4 (5.6) rTMS: 7.9 (7.1) <i>P</i> = NS</p> <p>3-month relapse, number (%) ECT: 2 (10) rTMS: 1 (5) <i>P</i> = NS</p> <p>6-month relapse, number (%) ECT: 4 (20) rTMS: 4 (19) <i>P</i> = NS</p>

ECT = electroconvulsive therapy; GAS = Global Assessment Scale; HAM-D₁₇ = Hamilton Rating Scale for Depression, 17-item instrument; n = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar

Two additional RCTs compared ECT with rTMS in a mixed population of unipolar and bipolar depression. One RCT compared 6-month remission rates for ECT and rTMS in 46 patients referred for ECT to treat a major depressive episode (Table 36).⁶¹⁻⁶³ Patients were not required to be treatment resistant, although on average patients had more than two previous treatment failures following adequate courses of medication—mean number (standard deviation) of failed treatments: ECT, 2.5 (1.4); rTMS, 2.4 (1). A small percentage of included participants had diagnoses of bipolar depression (9%) or psychosis (15%). Patients continued their usual medical care and psychotropic medications, with no changes in medication allowed during their active treatment. ECT was administered twice weekly. The number of ECT treatments was based on response, as determined by the referring physicians. High-frequency rTMS was administered for 15 consecutive weekday sessions. At the end of treatment, HAM-D₁₇ scores were statistically significantly lower for the ECT group than for the rTMS group (*P* = 0.002), and the ECT group had a greater percentage of patients in remission (59.1% vs. 16.7%, respectively; *P* = 0.006). After 6 months of followup, HAM-D₁₇ scores and remission rates were similar for the ECT and rTMS patients.

A second RCT reported 4 weeks of followup after 3 weeks of acute treatment with ECT (n=30) or rTMS (n=30). Patients were not specified to be treatment resistant, but were being referred for ECT for MDD. Most participants had unipolar depression, although 13 percent had bipolar depression. Patients continued their usual medications, with no changes in medication allowed during their active treatment. At the end of 3 weeks of acute treatment, ECT was significantly better than low-frequency rTMS (*P* = 0.035). At the end of 7 weeks (4 additional weeks), response and remission rates were not statistically significantly different for ECT

Table 36. Maintenance of remission of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
McLoughlin et al., 2007 ⁶¹ Eranti et al., 2007, ⁶² Knapp et al., 2008 ⁶³ RCT Fair	<p>ECT (n = 22; n = 12 for 6-month followup) 82% bilateral, mean sessions 6.3 (SD: 2.5)</p> <p>rTMS (n = 24; n = 4 for 6-month followup) High frequency, 15 sessions</p> <p>Treatment strategy Augmentation</p> <p>Definitions Remission: HAM-D₁₇ ≤ 8 Response: HAM-D₁₇ reduction ≥ 50% Measured at end of treatment and 6 months after baseline (maintenance of remission)</p>	<p>HAM-D₁₇ Baseline, mean (SD) ECT: 24.8 (5.0) rTMS: 23.9 (7.0) P = NS</p> <p>End of treatment, mean (SD) ECT: 10.7 (NR) rTMS: 18.5 (NR) P = 0.002</p> <p>6-month (from baseline), mean (SD) ECT: 13.8 (NR) rTMS: 13.5 (NR) P = NS</p> <p>End of treatment remission, n (%) ECT: 13 (59.1) rTMS: 4 (16.7) P = 0.006</p> <p>6-month remission, n (%) ECT: 6 (50) rTMS: 2 (50) P = NR</p>
Hansen et al., 2010 ⁶⁰ RCT Fair	<p>ECT (n = 30) 100% unilateral, 9 sessions</p> <p>rTMS (n = 30) Low frequency, 15 sessions</p> <p>Treatment strategy Augmentation</p> <p>Definitions Response: HAM-D₁₇ reduction ≥ 50% Remission: HAM-D₁₇ < 12 Measured at end of treatment (week 3) and after 4 additional weeks (week 7)</p>	<p>HAM-D₁₇ Baseline, median (range) ECT: 24 (16-34) rTMS: 24 (14-38) P = NS</p> <p>Week 3 remission rate (95% CI) ECT: 0.53 (0.34-0.72) rTMS: 0.27 (0.12-0.46) P = 0.035</p> <p>Week 7 remission rate (95% CI) ECT: 0.57 (0.37-0.75) rTMS: 0.40 (0.23-0.59) P = 0.200</p>

ECT = electroconvulsive therapy; HAM-D₁₇ = Hamilton Rating Scale for Depression, 17-item instrument; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

compared with rTMS ($P = 0.200$). Response and remission rates continued to improve for the rTMS group, while no further reduction in HAM-D scores were observed in the ECT group (HAM-D score change from weeks 3–7; $P = 0.001$ and $P = 0.78$, respectively). However, these results are potentially confounded by increases in antidepressant dose and switching from rTMS to ECT during the followup period; 12 of 23 rTMS nonresponders switched to ECT during the 4-week followup.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT in patients in this group. No sham-controlled studies addressed this population for ECT, VNS, or CBT. Two rTMS RCTs using a sham procedure as control addressed maintenance of remission (longer term relapse rates) in an MDD population (Table 37).^{69,77,99}

Table 37. Maintenance of remission of rTMS versus sham: Tier 1, MDD

Author, year Design Quality	Intervention and Sample Size Study Details	Results on HAM-D Instruments
Avery et al., 2006 ^{77,99} RCT Fair	<p>rTMS (n = 35, 11 for relapse followup) High frequency, 15 sessions over 4 weeks</p> <p>Sham (n = 33, 2 for relapse followup)</p> <p>Treatment strategy Mixed-within group differences 31% of rTMS group and 27% of control group continued taking medications</p> <p>Definitions Remission definition: HAM-D₂₁ < 10 Response: HAM-D₁₇ reduction ≥ 50% Remission: HAM-D₁₇ < 8 Relapse: not defined Measured at end of treatment (visit 16) and reassessed 1 week later (visit 17); Response could enter 6-month followup</p>	<p>HAM-D₁₇ 6-month relapse, n (%) rTMS: 6 (54.5); 1 lost to followup Sham: 1 (50); 1 lost to followup P = NR</p>
Boutros et al., 2002 ⁶⁹ RCT Fair	<p>rTMS (n = 12, 6 for followup phase) High frequency, 10 sessions</p> <p>Sham (n = 9, 1 for followup phase)</p> <p>Treatment strategy Augmentation</p> <p>Definitions Response1 definition: >30% decrease in HAM-D₂₅ Response2 definition: ≥50% decrease in HAM-D₂₅**calculated from table Relapse: HAM-D₂₅ ≥ baseline score ± 10% Relapse measured up until 20 weeks</p>	<p>HAM-D₂₅ 20-week relapse, n (%) rTMS: 4 (66.6); 1 lost to followup Sham: 1/1 (100) P = NS</p>

HAM-D = Hamilton Rating Scale for Depression, 17-item instrument or 25-item instrument; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Subjects in both rTMS trials were allowed to remain on psychotropic medications. The slightly larger and more recently conducted trial (n = 68)^{77,99} compared 15 sessions of high-frequency rTMS at 110 percent motor threshold with 1,600 pulses per session with a similarly delivered sham rTMS. At the end of treatment, responders could enter a 6-month followup to assess relapse. The smaller trial (n = 21)⁶⁹ compared 10 sessions of high-frequency rTMS at 80 percent motor threshold with 800 pulses per session with a similarly delivered sham rTMS. At the end of treatment responders could enter a 20-week followup.

In both trials, significantly more rTMS-treated than sham-treated participants were classified as responders: respectively, 30.6 percent versus 6.1 percent (P = 0.008);^{77,99} and 50 percent versus 22 percent (P < 0.05)⁶⁹. Of the small number of responders in these trials followed for maintenance of response, more than 50 percent relapsed; no statistically significant differences in relapse rates were observed between the rTMS and sham groups.

MDD/Bipolar

One trial addressed maintenance of remission with rTMS versus sham therapy in a mixed MDD-bipolar population (Table 38).⁸² Unlike other studies comparing rTMS and sham stimulation, in this study all patients also received a social support intervention. All patients had treatment failures of at least two separate trials of a minimum of 4 weeks' duration at therapeutic dosages of antidepressant medications. Two of 48 enrolled patients had bipolar disease; both were randomized to the right rTMS group. Participants were randomized to left- or right-sided delivery of 10 sessions of rTMS or sham and followed for 3 months. At the end of active treatment as well as at 1- and 3-month followup, differences in mean HAM-D scores were not statistically significantly different for rTMS compared with sham. Statistically significant differences were noted between right and left rTMS and right and left sham, consistently showing better reductions for right-sided compared with left-sided delivery ($P = 0.012$). It is possible that the inclusion of a social support intervention may have muffled the effects of rTMS in this study.

Table 38. Maintenance of remission of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Results on HAM-D Instruments
Triggs et al., 2010 ⁸² RCT Fair	<p>rTMS (n = 16 right(r); n = 18 left(l)) High frequency, 10 sessions over 2 weeks</p> <p>Sham (n = 14)</p> <p>Treatment strategy Augmentation</p> <p>Definitions Response: HAM-D₂₄ reduction $\geq 50\%$ Measured at end of treatment and 1 and 3 months after baseline (maintenance of response)</p>	<p>HAM-D₂₄ End of treatment, mean (SD) rTMS(r): 13.7 (7.6) rTMS(l); 19.8 (9.1) Sham: 17.7 (10.4) $P = 0.14$</p> <p>1 month, mean (SD) rTMS(r): 11.2 (7.5) rTMS(l); 18.2 (9.8) Sham: 19.7 (11.3) $P = NS$</p> <p>3 months, mean (SD) rTMS(r): 11.7 (9.3) rTMS(l); 16.3 (11.5) Sham: 17.9 (11.6) $P = NS$</p>

HAM-D₂₄ = Hamilton Depression Scale, 24 item; n = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No studies assessing maintenance of remission directly compared ECT, rTMS, VNS, and CBT. Two trials were relevant for this topic in this patient population (Table 39).

Two RCTs compared rTMS with sham rTMS and assessed maintenance of remission following active treatment.^{86,87,115,116} One trial randomized 30 participants to 10 sessions of 3 different rTMS strategies (10 subjects in each group) and 15 participants to 10 sessions of similar sham strategies (5 subjects in each group). The three treatment groups were high frequency delivered to the left dorsolateral prefrontal cortex (left high), low frequency delivered to the left dorsolateral prefrontal cortex (left low), and low frequency delivered to the right left dorsolateral

prefrontal cortex (right low). At the end of treatment, the left high and right low treatment groups had similar reductions in HAM-D₂₁ scores, and these differences were statistically significantly greater than the left low and sham groups ($P < 0.001$). These differences remained after 2 weeks of followup; no left low- or sham-treated participants were in remission after 2 weeks, whereas

Table 39. Maintenance of remission of rTMS versus sham: Tier 2, MDD

Author, Year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
<p>Stern et al., 2007⁸⁶ RCT Fair</p>	<p>High rTMS (n = 10) High frequency, 10 sessions</p> <p>Low-left rTMS (n = 10) Low frequency (1 Hz), Left-DLPFC, 10 sessions</p> <p>Low rTMS (n = 10) Low frequency, 10 sessions</p> <p>Sham (n = 15)</p> <p>Treatment strategy Switch</p> <p>Definitions Remission definition HAM-D₂₁ ≤ 10 Response and remission measured at end of treatment (2 weeks) and after 1 and 2 weeks of followup</p>	<p>HAM-D₂₁ End of treatment score, mean (SD) Left high rTMS: 15.1 (6) Left low rTMS: 27.6 (5.9) Low rTMS: 15.8 (4.8) Sham: 26.7 (3.6) $P < 0.001$</p> <p>2-week followup score, mean (SD) Left high rTMS: 13.4 (5.6) Left low rTMS: 26.6 (3) Low rTMS: 14.9 (5.9) Sham: 26.8 (2.3) $P < 0.001$</p> <p>End of treatment response, n (%) Left high rTMS: 5 (50) Left low rTMS: 0 (0) Low rTMS: 5 (50) Sham: 0 (0%) $P = \text{NR}$</p> <p>2-week followup response, n (%) Left high rTMS: 4 (40) Left low rTMS: 0 (0) Low rTMS: 6 (60) Sham: 0 (0) $P = \text{NR}$</p> <p>End of treatment remission, n (%) Left high rTMS: 3 (33.3) Left low rTMS: 0 (0) Low rTMS: 1 (10) Sham: 0 (0) $P = \text{NR}$</p> <p>2-week followup remission, n (%) Left high rTMS: 4 (40) Left low rTMS: 0 (0) Low rTMS: 3 (33.3) Sham: 0 (0) $P = \text{NR}$</p>

Table 39. Maintenance of remission of rTMS versus sham: Tier 2, MDD (continued)

Author, Year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
O'Reardon et al., 2007, ⁸⁷ Janicak et al., 2007, ¹¹⁵ Solvason et al., 2007 ¹¹⁶ Janicak et al., 2010 ¹¹⁹ RCT Fair	<p>rTMS (n = 99 for followup phase) High frequency, up to 30 sessions; rescue add-on permitted for symptom breakthrough (deterioration of CGI-S by 1 point over 2-week interval) during continuation</p> <p>Sham (n = 21 for followup phase)</p> <p>Treatment strategy Acute treatment switch; continuation rescue was augment to current pharmacotherapy</p> <p>Definitions Relapse defined as recurrence of the full syndrome of major depression per DSM-IV over ≥ 2 weeks: HAM-D₁₇ ≥ 20; CGI-S ≥ 4</p>	<p>HAM-D₁₇ Remission Score at week 4, mean (SD) rTMS: -14.6 (6.16) Sham: -14.4 (6.11)</p> <p>Relapse Rates: Continuation at week 24, n (%) rTMS: 10 (10) Sham: 3 (13.6) P = NR</p>

DLPFC = dorsolateral prefrontal cortex; HAM-D = Hamilton Rating Scale for Depression, 21-item instrument; Hz = hertz; MT = motor threshold; n = number; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

40 percent of left high- and 33 percent of right low-treated participants were in remission after 2 weeks ($P = \text{NR}$).

Another trial followed 120 patients over 24 weeks to assess the durability of acute response to high-frequency rTMS or sham.^{87,115,116,119} The acute phase of this trial was a switch strategy that randomized 155 severely depressed participants to active rTMS and 146 severely depressed participants to sham rTMS.⁸⁷ After 6 weeks of acute treatment, 44 active rTMS-treated patients and 23 sham rTMS-treated patients were classified as responders. These patients entered a 3-week taper phase, and then began 24 weeks of open-label continuation followup.¹¹⁵ The remaining nonresponders were offered open-label rTMS, and an additional 32 participants from the original active rTMS group and 49 participants from the original sham rTMS group responded. Of these, durability of response was compared in 99 active rTMS responders and 21 sham responders. Open-label rTMS was permitted as rescue augmentation to the current antidepressant regimen for symptom breakthrough. Relapse was defined as recurrence of the full syndrome of major depression per DSM-IV criteria observed over at least 2 weeks. After 24 weeks, 10 (10%) active rTMS-treated participants relapsed and 3 (13.6%) sham-treated participants relapsed ($P = \text{NR}$).

MDD/Bipolar

One RCT compared rTMS with a sham procedure in 20 patients who had at least one adequate pharmacological failed trial during the current or previous episode (Table 40).⁸⁸ The majority of included patients (80 percent) had two or more failed medication trials during the current episode. The inclusion criteria allowed patients to have comorbid psychiatric diagnoses provided that the onset occurred after the development of major depression and that the symptoms of major depression were more prominent. This resulted in the inclusion of one patient (assigned to sham) with a bipolar II, depressed diagnosis; the remainder had unipolar major depression. Patients assigned to active treatment (n = 10) received 10 sessions of high-frequency rTMS applied to the left dorsolateral prefrontal cortex. Patients assigned to the sham

intervention (n = 10) received 10 sessions using the same device with the coil angled 30 to 45 degrees off the scalp and the bottom of the coil elevated 0.5 centimeters from the scalp. Response was defined by a 25-item HAM-D score ≤ 15 and a reduction in this score of 50 percent or more from baseline. At the end of treatment, one rTMS-treated patient (10%) and no sham-treated patients were categorized as responders ($P = 0.09$). The rTMS responder remained a responder during 2 months of followup.

Table 40. Maintenance of remission of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention and Sample Size Study Details	Maintenance of Remission
Berman et al., 2000 ⁸⁸ RCT Fair	rTMS (n = 10; 1 for followup phase) High frequency, 10 sessions Sham (n = 10; 0 for followup phase) Treatment strategy Switch Definitions Response: HAM-D ₂₅ ≤ 15 and reduction from baseline $\geq 50\%$ Response measured at end of treatment (2 weeks) and up to 2 months after treatment	HAM-D₂₅ End of treatment score, mean (SD) rTMS: 24.6 (NR) Sham: 36.4 (NR) $P < 0.01$ End of treatment response, n (%) rTMS: 1 (10) Sham: 0 (0) $P = 0.09$ 2-month maintained response, n (%) rTMS: 1 (100) Sham: 0 (100) $P = \text{NR}$

HAM-D = Hamilton Rating Scale for Depression, 25-item instrument; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

No trial addressed maintenance of remission with rTMS versus sham therapy in an MDD-only population.

MDD/Bipolar

One RCT compared rTMS with a sham procedure in 19 patients with unspecified drug resistance (Table 41).⁹⁰ The majority of patients had unipolar major depression, although 16 percent had bipolar depression. Patients assigned to active treatment (n = 12) received 5 sessions of high-frequency rTMS applied daily to the left prefrontal cortex for 5 days. Patients assigned to the sham intervention (n = 7) received five similar sessions with the coil placed perpendicular to the scalp surface without direct contact. Depression severity was measured by the 24-item HAM-D and the 21-item BDI. At the end of treatment, rTMS-treated patients had significantly lower HAM-D and BDI scores than sham-treated patients ($P < 0.001$). This statistically significant difference was maintained through week 4 (3 weeks after end of treatment), but patients reverted to the previous depressed mood at week 12 ($P = \text{NS}$).

Table 41. Maintenance of remission of rTMS versus sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Bortolomasi et al., 2006 ⁹⁰ RCT Fair	<p>rTMS (n = 12) High frequency, 5 sessions</p> <p>Sham (n = 7)</p> <p>Treatment strategy Augmentation</p> <p>Definitions Outcome = change in HAM-D₂₄ and BDI₂₁</p>	<p>HAM-D₂₄ Baseline score, mean (SD) rTMS: 25.17 (NR) Sham: NR (NR) <i>P</i> = NR</p> <p>End of treatment (at week 1), mean (SD) rTMS: 11.33 (NR) Sham: 18.29 (NR) <i>P</i> < 0.001</p> <p>At week 4, mean (SD) rTMS: 11.42 (NR) Sham: 19.14 (NR) <i>P</i> < 0.001</p> <p>At week 12, (NR) Both groups reverted to depressed mood <i>P</i> = NS</p> <p>BDI₂₁ Results similar to HAM-D₂₄</p>

BDI₂₁ = Beck Depression Inventory, 21-item instrument; HAM-D₂₄ = Hamilton Rating Scale for Depression, 24-item instrument; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Cognitive Behavioral Therapy Versus Usual Care

Tier 1: Patients With two or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with CBT versus usual care in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Tier 2: Patients With one or More Treatment Failures

MDD-Only

No trial addressed maintenance of remission with CBT versus usual care in an MDD-only population.

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Tier 3: Patients With Probable Treatment Resistance

MDD-Only

One trial, lasting 68 weeks and involving 158 participants, compared relapse rates for CBT and sham treatment (Table 42).^{95,96,120,121} All participants received usual clinical management and antidepressant drug continuation throughout the study. Participants also were followed for an additional 4.5 years.¹²¹ In the CBT group, 80 participants received 16 sessions over a 20-week period, plus two booster sessions approximately 6 to 14 weeks later. The sham group was seen by a psychiatrist every 4 weeks during the first 20 weeks and then every 8 weeks thereafter. The relapse outcome was defined by two criteria. The first criterion was meeting the criteria from the Diagnostic and Statistical Manual, Version 3, Revised for major depression for 1 month or more, with a HAM-D₁₇ score of 17 or higher on two successive visits 1 week apart. The second criterion, which was applied only during the followup phase, was persistent symptoms for 2 months or more with a HAM-D₁₇ score of 17 or higher at both visits. At the end of treatment (i.e., 20 weeks) and at 44 weeks, relapse rates were similar between CBT- and sham-treated participants. At the end of 68 weeks, significantly more sham-treated participants than CBT-treated participants had relapsed. Based on the combined definition of major depression with persistent symptoms, 29 percent of CBT-treated participants and 47 percent of sham-treated participants had relapsed by 68 weeks (hazard ratio for relapse 0.54; 95% CI, 0.32-0.93; $P = 0.02$). In a followup study of 135 participants over a total of 6 years, recurrence curves suggested the effects of CBT were persistent for up to 3.5 years, although actuarial recurrence rates were only statistically significantly different through 20 weeks after randomization.¹²¹

Table 42. Maintenance of remission of CBT versus usual care: Tier 3, MDD

Author, year Design Quality	Intervention, Sample Size, and Study Details	Maintenance of Remission
Paykel et al., 1999 ⁹⁵ Scott et al., 2000; ⁹⁶ Scott et al., 2003 ¹²⁰ Paykel et al., 2005 ¹²¹ RCT Fair	<p>CBT plus clinical management (n = 80) 16 session during 20 weeks</p> <p>Clinical management alone (n = 78)</p> <p>Treatment strategy Augmentation</p> <p>Definitions Relapse: HAM-D₁₇ ≥ 17 on 2 successive visits 1 week apart, OR, at followup for ≥ 2 months</p>	<p>Relapse Rates, number (%) Major depression alone At 20 weeks CBT: 9 (11) Sham: 14 (18) P = NR At 44 weeks CBT: 15 (19) Sham: 25 (31) P = NR At 68 weeks CBT: 18 (22) Sham: 29 (36) P = 0.08 Hazard Ratio: 0.58 (95% CI, 0.37-1.07)</p> <p>Relapse Rates, number (%) Major depression plus symptoms At 20 weeks CBT: 8 (10) Sham: 14 (18) P = NR At 44 weeks CBT: 19 (24) Sham: 31 (40) P = NR At 68 weeks CBT: 23 (29) Sham: 37 (47) P = 0.02 Hazard Ratio: 0.54 (95% CI, 0.32-0.93)</p> <p>Recurrence rate in long-term followup At 120 weeks CBT: 27(38) Sham: 28(43) P = 0.25 At 275 weeks CBT: 42(60) Sham: 42(65) P = 0.33</p>

CBT = cognitive behavioral therapy; CI = confidence interval; HAM-D₁₇ = Hamilton Rating Scale for Depression, 17-item instrument

MDD/Bipolar

No trial addressed maintenance of remission with CBT versus usual care in an MDD/bipolar mix population.

Key Question 3: Efficacy or Effectiveness for Treating Treatment-Resistant Depression for Particular Symptom Subtypes

Overview

This KQ focused on the comparative benefit of treatment for patients with TRD and an accompanying symptom subtype. Specifically of interest were symptom groups such as

psychosis, catatonia, or melancholy, subtypes that can accompany depression and which are often used to inform clinical interventions. We identified no studies that address this question in TRD (Tier 1) patients. However, a consideration of evidence from all tiers identified one relevant Tier 3 trial, reported in two articles.^{118,122} The study was a head-to-head comparison of ECT and rTMS in psychotic and nonpsychotic patients with TRD. Though the study was rated poor, we include it here because it provides some evidence on the efficacy of rTMS in patients with TRD and psychosis.

Strength of Evidence: Tier 1 (TRD)

We identified no eligible Tier 1 studies.

Key Points

The one study available on this topic^{118,122} was rated poor quality and involved a Tier 3 population with a primary finding that ECT produced significantly better outcomes than rTMS. A secondary analysis indicated that the presence of psychotic symptoms may have influenced the effect of these two interventions: psychotic patients appeared to have better outcomes with ECT than with rTMS. In nonpsychotic patients, the effect of the two interventions was similar. Of note, however, the differential use of psychotropic medications during the course of the trial may have biased the results in favor of ECT. The two groups were being treated with different drugs at baseline; ECT patients were allowed to continue any medication, including antipsychotics, at a stable rate, but the rTMS patients were limited to clonazepam.

Detailed Analysis

ECT Versus rTMS

There were no eligible studies in Tier 1 or 2. In Tier 3, there were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies in an MDD-only population and one study (two articles) in an MDD/bipolar mix population.

MDD-Only

There were no eligible studies.

MDD/Bipolar Mix

The study was undertaken with 40 inpatients and outpatients who had been referred for ECT; detailed information is available in the evidence table in Appendix D. The investigators randomized patients to either ECT or rTMS. Of those receiving ECT, 10 had TRD only and 10

had TRD and psychosis; of those receiving rTMS, 11 had TRD only and 9 had TRD and psychosis. The primary comparison was the change in HAM-D score at 2 weeks and end of treatment (approximately 4 weeks), with higher scores better than lower scores.

Overall, patients responded better to ECT than to rTMS ($P < 0.05$). With regard to psychotic versus nonpsychotic patients, the study reported two important findings. First, in nonpsychotic patients, ECT and rTMS were equally effective. HAM-D₁₇ scores at the end of treatment for ECT and rTMS were 13.9 and 11.0 ($P = \text{NS}$), respectively. Second, in psychotic patients, ECT appeared to be more effective than rTMS; HAM-D₁₇ scores at the end of treatment were 8.4 and 20.8 ($P = 0.01$), respectively.

This study has limitations for our KQ because treatment bias restricted applicability to our population of interest. The ECT group had been allowed to continue on any psychotropic medication, including antipsychotic medications, at a stable dose, while the rTMS group had all their psychotropic medications discontinued although they were prescribed clonazepam (a benzodiazepine derivative with anticonvulsant, muscle relaxant, and anxiolytic properties) to reduce anxiety, limit insomnia, and help prevent seizures. This variation introduced a treatment, or co-intervention, bias. In this sample, 25 patients had been treated unsuccessfully 2 or more times and 15 patients either had been treated unsuccessfully only one time or had had no treatment failures; nonetheless, all had been referred for ECT, and so we classified them as Tier 3 (probable treatment resistance).

Key Question 4: Organization of Safety, Adverse Events, and Adherence

KQ 4 contains information addressing safety, adverse events, and adherence in the use of nonpharmacological treatments to treat TRD. The following section is split into four segments, each comparing the effects of the four nonpharmacologic interventions (ECT, rTMS, VNS, CBT/IPT) with each other (head-to-head comparisons) or with control interventions (e.g., sham procedures) but focusing on a different outcome. KQ 4a addresses the impact on cognitive functioning. KQ 4b examines specific adverse events (other than cognitive functioning) that were assessed systematically. The next two segments use two measures of study withdrawals. KQ 4c examines general tolerability to the treatments by using withdrawals specifically due to adverse events. The final segment, KQ 4d, examines adherence by examining withdrawals for any reason (overall withdrawals), as only a few studies measured adherence as an outcome.

Key Question 4a: Cognitive Functioning—Overview

This KQ concerns the issue of whether the four nonpharmacologic interventions (ECT, rTMS, VNS, CBT/IPT) compared with each other (head-to-head comparisons) or against control interventions (e.g., sham procedures) have different effects on cognitive functioning. Cognitive functioning is measured in several domains, such as the Mini-Mental Status Examination (MMSE) and various intelligence, learning, or memory tests such as the Rey Auditory Verbal Learning Test (RAVLT), the Wechsler Adult Intelligence Scale (WAIS), and the Cambridge Examination for Mental Disorders of the Elderly (and the cognitive, self-contained part of the Cambridge instrument denoted CAMCOG). Appendix F lists the major instruments used to detect or diagnose cognitive impairments across a wide range of faculties.

We included 11 studies of either good or fair quality; of these, 5 compared ECT to rTMS, 5 evaluated rTMS against a sham procedure, and one compared ECT to ECT plus rTMS (Table 43). Only one had cognitive functioning as a

Table 43. Number of good- and fair-quality studies by TRD tier and diagnostic mix for KQ 4a

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	2	0
ECT vs. rTMS	Tier 2: ≥ 1 treatment failure	1	0
ECT vs. rTMS	Tier 3: Probable	0	2 additional
ECT vs. ECT + rTMS	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	3	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2 additional	0

ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation, vs. = versus

primary outcome of interest. All tested cognitive functioning effects in the acute phase of treatment and did not address long-term or cumulative effects of the interventions. In the detailed analysis section below, we consider first the studies involving only patients with MDD and then the mixed MDD/bipolar populations. For studies that did not report sufficient information to determine if the population was MDD-only or a mixed MDD/bipolar population, we placed them in the mixed MDD/bipolar section. Information is presented for the three tiers used throughout this report: Tier 1, two or more treatment failures; Tier 2, one or more treatment failures; and Tier 3, “probable” treatment resistance.

When considering only studies conducted in Tier 1 patients with MDD, there were two head-to-head trials of ECT versus rTMS,^{58,123} one trial comparing ECT to ECT plus rTMS,⁶⁴ and three rTMS versus sham studies (four articles).^{73,76,77,99}

Additional eligible studies were found in Tiers 2 and 3. One head to head study was conducted in Tier 2 patients and compared ECT to rTMS.⁵⁹ Two studies (six articles) comparing rTMS to sham were conducted in Tier 2 patients with MDD.^{84,85,87,115,116,119,124,125} Two head-to-head studies (four articles) in Tier 3 compared ECT with rTMS.^{61-63,126}

Strength of Evidence: Tier 1 (TRD)

Table 44 shows the evidence for studies limited to Tier 1, patients that have two or more previous treatment failures for depression. The two studies that compare ECT versus rTMS, one an RCT and the other a cohort study, provide insufficient evidence to determine whether there is a difference in cognitive outcomes between ECT and rTMS during the acute phase of treatment. In the three studies that populate Tier 1 on comparisons of rTMS versus sham, there is insufficient evidence to assess the impact of rTMS on cognitive functioning during acute phase treatment.

Table 44. Strength of Evidence: impact on cognitive functioning – Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results Strength of Evidence
ECT vs. rTMS	2; 72	Medium 1 RCT, and 1 prospective cohort study Both fair	Inconsistent	Direct	Imprecise	Some evidence suggests no difference between treatments, whereas some evidence suggests that ECT has a deleterious impact on cognitive functioning compared to rTMS Insufficient
ECT vs. ECT plus rTMS	1;22	High 1 RCT Fair	Unknown	Indirect	Imprecise	Insufficient
rTMS vs. sham	3; 101	Medium 3 RCTs, 1 good, 2 fair	Inconsistent	Indirect	Imprecise	Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham Insufficient

ECT = electroconvulsive therapy; RCT(s) = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 4a: Cognitive Functioning—Key Points

Limited evidence addressed the impact of these procedures on cognitive functioning; no evidence was available for VNS or CBT/IPT.

Overall, we included 11 studies (20 articles) that examined cognitive functioning during acute phase treatment.^{58,59,61-64,73,76,77,84,85,87,99,115,116,119,123-126} Nine studies were limited to patients with MDD-only, 4 comparing ECT with rTMS,^{58,59,123,126} and 5 studies (12 articles) comparing rTMS with sham.^{73,76,77,84,85,87,99,115,116,119,124,125} Two studies (five articles) included a mixed (20 percent or less bipolar) population; one study (three articles) compared ECT with rTMS,⁶¹⁻⁶³ and the second study compared ECT versus ECT plus rTMS.⁶⁴

Included studies are mostly small; samples had a mean of 35 participants per study and ranged from 15⁷⁶ to 68^{77,99} participants per study with the exception of one study that had 325 participants.^{87,115,116,119,124,125} Overall, cognitive functioning impacts did not differ much between treatment groups. Some tests did show a statistically significant difference but not necessarily a clinically meaningful one.^{73,76,77,84,85,99}

Any negative cognitive functioning impact that did occur with ECT faded away relatively quickly. Differences tended to dissipate to insignificance between end of treatment assessments and subsequent assessments (mean 8.8 days,¹²⁶ 2 weeks,¹²⁶ and 6 months⁶¹⁻⁶³).

Key Question 4a: Cognitive Functioning—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Magnetic Stimulation

There were two studies, an RCT and a prospective cohort study, in Tier 1. There was one study in Tier 2. In Tier 3, there was one RCT and one prospective cohort study.

Tier 1

There were two studies, an RCT and a prospective cohort study.

MDD-Only

Two studies, shown in Table 45, provided data on the head-to-head comparison of ECT versus rTMS.^{58,123} One was an RCT that compared right unilateral ECT for 2 weeks in 20 patients with high-frequency rTMS in 22 patients.⁵⁸ At the end of treatment at 2 weeks and after a 2-week followup, for a total of 4 weeks, the groups did not differ on cognitive tests that included the Weschler Adult Intelligence Scale, Weschler Memory Scale, and the Rivermead Behavioral Memory Test.

The other was a prospective cohort study of 30 subjects.¹²³ The study used RAVLT, Memory for Persons Test, Autobiographical Memory Interview, Four card task, and the Squire Subjective Memory Questionnaire (SSMQ) to test cognitive functioning. Several of the cognitive tests showed a statistically significant difference between the ECT and rTMS groups, with ECT having a deleterious effect on cognitive functioning compared to rTMS. Two sections of the RAVLT showed significant differences in post-treatment measures in favor of rTMS: recall after interference (ECT 3.9 vs. rTMS 1.8; $P < 0.01$), recall after delay (ECT 4.2 vs. rTMS 2.4; $P < 0.05$). Differences were also found in retrograde memory function. The ECT group made significantly more errors than those in the rTMS group in recognizing words learned before treatment (ECT 5.0 vs. rTMS 1.1, $P = 0.025$). After treatment, ECT recipients also recalled significantly fewer items (0.4) from the visual card task administered before treatment than did the rTMS group (1.4, $P = 0.012$). Subjective memory, measured using the SSMQ, improved in the rTMS group from -16.8 to 3.8 and stayed similar in the ECT subjects, changing from -20.7 to -15.2 at endpoint ($P < 0.05$ for rTMS vs. ECT).

MDD/Bipolar mix

There were no eligible studies.

Tier 2

One fair rated RCT comparing rTMS to ECT in 40 MDD only patients is presented in Table 46.⁵⁹ There were no differences in cognitive functioning as measured by the MMSE.

Table 45. Impact on cognitive functioning of ECT versus rTMS: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Rosa et al, 2006 ⁵⁸ RCT Primary endpoint was after up to 4 weeks of active treatment Fair	ECT (n = 20) % bilateral NR, mean sessions 10 (SD 1.5) rTMS (n = 22) High frequency, 10-20 sessions (2-4 weeks)	WAIS-R, subsections of WMS (digit span) and RBMT:: ECT vs. rTMS: no significant differences

Table 45. Impact on cognitive functioning of ECT versus rTMS: Tier 1, MDD (continued)

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
<p>Schulze-Rauschenbach et al., 2005¹²³ Prospective cohort Outcomes measured 8.8 days on average after last treatment Fair</p>	<p>ECT (n = 14) Right unilateral txt for 2 weeks rTMS (n = 16) High frequency, mean 10.8 sessions (SD 1.4)</p>	<p>Learning and Anterograde Memory with AVLT: Recall after interference: Before treatment ECT: 2.8 (2.2) vs. rTMS: 3.2 (1.9) 1 week after treatment ECT: 3.9 (1.9) vs. rTMS: 1.8 (2.0), <i>P</i> < 0.01 Recall after delay: Before treatment ECT: 2.4 (1.8) vs. rTMS: 3.2 (1.6) 1 week after treatment ECT: 4.2 (1.6) vs. rTMS: 2.4 (2.0), <i>P</i> < 0.05 Other AVLT subscales or the Memory for Persons Test (MPT): No significant differences Retrograde memory with AVLT Recall: No difference on recall or recognition hits Recognition false alarms 1 week after treatment: ECT: 5.0 (3.0) vs. rTMS: 1.1 (1.1), <i>P</i> < 0.05 Four-card task - Free recall: 1 week after treatment ECT: 0.4 (0.5) vs. rTMS: 1.4 (1.2), <i>P</i> < 0.05 Subjective memory with SSMQ: Before treatment ECT: -20.7 (19.0) vs. rTMS: -16.8 (16.9) 1 week after treatment ECT: -15.2 (25.2) vs. rTMS: 3.8 (11.8), <i>P</i> < 0.05</p>

AVLT = Auditory Verbal Learning Test; ECT = electroconvulsive therapy; MPT = memory persons test; n = number; NR = not reported; pt = patient; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SSMQ = Squire Subjective Memory Questionnaire; txt = treatment; vs. = versus; WAIS-R = Weschler Adult Intelligence Scale-Revised; WMS = Weschler Memory Scale

Table 46. Impact on cognitive functioning of ECT versus rTMS: Tier 2, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
<p>Grunhaus et al., 2003⁵⁹ RCT 2-4 weeks Fair</p>	<p>ECT (n = 20) 35% bilateral, mean sessions 10.25 (SD 3.1) rTMS (n = 20) High frequency, 20 sessions (4 weeks)</p>	<p>MMSE Baseline (SD) ECT: 25.8 (3.4) rTMS: 27.8 (3.0) Week 2 (SD) ECT: 26.3 (2.9) rTMS: 27.8 (3.0) End of treatment (SD) ECT: 27.1 (2.5) rTMS: 28.0 (1.8) Group by time interaction, <i>P</i> = NS</p>

ECT = electroconvulsive therapy; NS = not significant; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; vs. = versus

Tier 3

There were no MDD studies and in an MDD/bipolar mix there was one RCT and one prospective cohort study (Table 47).

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One RCT and one prospective cohort study provide head-to-head evidence comparing rTMS with ECT for mixed MDD/bipolar populations, as shown in Table 47.^{61-63,126} The RCT compared high-frequency rTMS (n = 22, for 15 sessions) versus ECT (n = 24, mean number of sessions 6.3, range 2-10, based on physicians' opinion).⁶¹⁻⁶³ The primary cognitive tests included the MMSE and CAMCOG. There were no statistically significant differences in MMSE scores or total CAMCOG scores between the ECT group and the rTMS group. In addition, most of the CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory) showed no significant differences; but subjects treated with ECT did statistically significantly better than those treated with rTMS on the attention and orientation subscale (respectively, an increase of 1.1 from baseline versus a decline of 1.2 from baseline; $P = 0.004$).

Table 47. Impact on cognitive functioning of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Quality	Intervention and Sample Size Study Details	Outcomes
<p>McLoughlin et al., 2007⁶¹ Eranti et al., 2007⁶² and Knapp et al., 2008⁶³ RCT Primary endpoint is end of treatment (at clinicians' discretion for ECT group, 3 weeks in rTMS) Good</p>	<p>ECT (n = 24) 82% bilateral rTMS (n = 22) High frequency, 15 sessions</p>	<p>CAMCOG attention and orientation subscale (max = 17), n (SD). Baseline ECT: 12.8 (3.2) rTMS: 14.7 (3.0) End of treatment ECT: 13.9 (3.6) rTMS: 13.5 (3.3) 6 mos ECT: 13.9 (3.5) rTMS: 13.4 (3.8) <i>P</i> = 0.004 CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory): No significant differences MMSE Baseline, n ECT: 16 rTMS: 22 Baseline, mean (SD) ECT: 24.3(3.6) rTMS: 25.7 (3.9) End of treatment/6-month followup, mean (SD) ECT: 25.6 (3.9)/25.4 (5.3) rTMS: 24.4 (5.3)/24.7 (4.8) Change at end of treatment, mean: ECT: 1.3 rTMS: -1.3 <i>P</i> < 0.08 Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects: No significant differences on the self-reported cognitive side effects.</p>

Table 47. Impact on cognitive functioning of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder (continued)

Author, Year Design Quality	Intervention and Sample Size Study Details	Outcomes
O'Connor et al., 2003 ¹²⁶ Prospective cohort Outcomes recorded at end of treatment and after 2 weeks of followup Fair	ECT (n = 14) unilateral, 3 times per week for 2 to 3 weeks rTMS (n = 14) high frequency, 10 sessions	RAVLT, Acquisition , mean (SD). Baseline ECT 43.78 (11.07) rTMS 43.71 (12.09). End of treatment ECT 29.14 (7.93) rTMS 43.00 (10.09) $P < 0.01$ 2 weeks later: ECT 46.92 (10.80) rTMS 44.07 (10.43) $P > 0.05$. RAVLT, Retention (15-item word list after a 20-minute delay interval), mean (SD) Baseline: ECT 8.07 (4.49) rTMS 9.76 (3.08) End of treatment: ECT 2.14 (1.99) rTMS 8.23 (2.80) 2 weeks later ECT 8.92 (4.14) rTMS 8.31 (4.07). TNET Baseline: ECT 64.30 (19.40) rTMS 55.63 (18.12). End of treatment: ECT 39.10 (13.21) rTMS 57.81(18.33) 2 weeks later: ECT 59.20 (20.67) rTMS 61.54 (19.12).

CAMCOG = Cambridge Examination for Mental Disorders in the Elderly; ECT = electroconvulsive therapy; MMSE = mini-mental state examination; mos = months; MT = motor threshold; n = number; NR = not reported; pps = pulses per second; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; Rtms = repetitive transcranial magnetic stimulation

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Within Tier 1, there was one RCT identified in an MDD patient population.

Tier 1

One RCT was conducted in 22 MDD patients (Table 48).⁶⁴ Memory problems, as measured by a single self-report question, were reported by twice as many patients in the ECT only group ($P = NS$).

Table 48. Impact on cognitive functioning of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Pridmore et al., 2000 ⁶⁴ RCT Outcomes measured after 2 weeks Fair	ECT (n = 11) 100% unilateral, 6 sessions ECT plus rTMS (n = 11) ECT: 100% unilateral (day 1), plus high frequency rTMS: (days 2-5) Repeated in week 2, 8 sessions	Memory complaints, n ECT: 9 ECT plus rTMS: 4 <i>P</i> = NS

ECT = electroconvulsive therapy; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

rTMS Versus Sham

Within Tier 1, three RCTs were identified in an MDD patient population, and no eligible studies in an MDD/bipolar mix population were identified. Two additional RCTs in an MDD patient population was identified when accounting for a Tier 2 definition. For MDD/bipolar patients, there were no eligible studies in Tier 2. Within Tier 3 in an MDD-only population, there were no eligible studies.

Tier 1

There were three RCTs in MDD patients and one RCT in patients with MDD/bipolar mix (Table 49).

MDD-Only

Three Tier 1 RCTs as shown in Table 49 evaluated rTMS against sham. The largest (n = 68) used high-frequency rTMS for 15 sessions and took cognitive measurements at baseline and following the final treatment. None of the tests showed a statistically significant difference between the two groups.^{77,99} The other two studies were smaller. One (n = 15) used high-frequency rTMS for ten sessions.⁷⁶ Tests included the RAVLT, Digit Symbol Test, Digit Span, and Stroop Test. Subjects in the two groups performed equally well with the exception of one measure of verbal memory, Trial 7 of RAVLT, in which subjects who received rTMS performed slightly better (12.7) than sham subjects (12.0, *P* < 0.05). Subjects treated with rTMS had mean neuropsychological tests that were either improved or equal to baseline levels of functioning. The other (n = 18) randomized subjects to five sessions of high-frequency rTMS, low frequency rTMS, or sham.⁷³ Between-group differences in changes in verbal memory performance were identified (Date NR, group by time interaction *P* = 0.006). The high-rTMS group showed improvement, the sham group showed deterioration, and the sham group showed no change in learning performance.

MDD/Bipolar mix

No eligible studies identified.

Table 49. Impact on cognitive functioning of rTMS versus sham: Tier 1, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
Avery et al., 2006 ^{77,99} RCT Outcomes measured after 2 weeks (except GOAT) Good	rTMS (n = 35) High frequency, 15 sessions over 4 weeks Sham (n = 33)	RAVLT, Digit Symbol Test and Digit Span (from the WAIS-R), Trail Making Test Parts A and B, MMSE, COWAT, the color Stroop Test: or GOAT, 5 minutes after each rTMS session: No significant differences -
Holtzheimer et al., 2004 ⁷⁶ RCT Outcomes measured after 2 weeks Fair	rTMS (n = 7) High frequency, 10 sessions Sham (n = 8)	Verbal Memory RAVLT, Trial 7, mean score (%): rTMS: 12.7 (2.1) Sham: 12.0 (2.3), <i>P</i> < 0.05. Neuropsychological measures of attention, verbal memory, psychomotor speed, and mental flexibility. Outcome measures: RAVLT subscales, Digit Symbol Test, Digit Span, and the Stroop Test: No significant differences
Padberg et al., 1999 ⁷³ RCT Outcomes measured after 1 week Fair	rTMS (n = 6) High frequency, 5 sessions Low-left rTMS (n = 6) 0.3 Hz, Left-DLPFC, 5 sessions Sham (n = 6)	Verbal memory performance Data NR Group by time interaction <i>P</i> = 0.006

COWAT = Controlled Oral Word Association Test; GOAT = Galveston Orientation and Amnesia Test; MMSE = mini-mental state examination; n = number; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; WAIS-R = Weschler Adult Intelligence Scale-Revised

Tier 2

There were two RCTs in MDD patient populations. Within an MDD/bipolar population there were no eligible studies (Table 50).

MDD-Only

One RCT (n = 20) (two articles) compared high-frequency rTMS intervals, for five sessions, with a sham procedure (see Table 50).^{84,85} Cognitive testing was completed at baseline and 3 days after the last (fifth) treatment. The rTMS group showed a significant improvement in Trail Making Test B test scores (baseline score: 87.22; endpoint: 58.59; *P* < 0.05), whereas scores for the sham group did not significantly change. The groups did not differ significantly on any other cognitive tests conducted (MMSE, Trail Making Test A, The Stroop Test, WAIS-R Digit Symbol; Controlled Oral Word Association Test, Boston Naming Test, Sentence Repetition, RAVLT, or Judgment of Line Orientation).

The second RCT (n = 325) compared high-frequency rTMS intervals, at 6 weeks, with a sham procedure (see Table 50).^{87,115,116,119,124,125} Cognitive testing was completed at baseline and at 6 weeks. The groups did not differ significantly on any of the cognitive tests conducted, which included the MMSE, the Buschke Selective Reminding Test, and the Autobiographical Memory Interview, nor were there significant changes within the groups from baseline to endpoint at 6 weeks.

Table 50. Impact on cognitive functioning for rTMS versus sham: Tier 2, MDD

Author, Year Design Endpoint Quality	Intervention and Sample Size Study Details	Outcomes
<p>O'Reardon et al., 2007;⁸⁷ Janicak, 2007;¹¹⁵ Sovason et al., 2007;¹¹⁶ Janicak et al., 2010¹¹⁹ Demitrack et al., 2009;¹²⁴ Janicak et al., 2008¹²⁵ RCT Outcomes measured at 6 weeks Good</p>	<p>rTMS (n = 165) High frequency,, 20-30 sessions Sham (n = 160)</p>	<p>MMSE Baseline (SD) rTMS: 28.5 (1.5) Sham: 28.4 (1.7) At 6 weeks- end of acute treatment (SD) rTMS: 28.8 (1.4) Sham: 28.4 (1.8) <i>P</i> = NS Short-term recall – BSRT Baseline (SD) rTMS: 47.6 (12.3) Sham: 47.4 (13.3) At 6 weeks- end of acute treatment (SD) rTMS: 49.4 (12.3) Sham: 49.1 (12.9) <i>P</i> = NS Amnesia Scores (AMI – Short Form) At 6 weeks – end of acute treatment (SD) rTMS: 88.5 (8.7) Sham: 89.8 (8.1) <i>P</i> = NS</p>
<p>Manes et al., 2001⁸⁴ and Moser et al., 2002⁸⁵ RCT Outcomes measured a mean of 3 days following 1 week treatment Fair</p>	<p>rTMS (n = 10) High Frequency 5 sessions Sham (n = 10)</p>	<p>MMSE, Trail Making Test A, The Stroop Test, WAIS-R Digit Symbol; COWAT, Boston Naming Test, Sentence Repetition, RAVLT (% of learned words recalled after delay), Judgment of Line Orientation: No significant differences Trail Making Test B, seconds Baseline rTMS: 87.22 Sham: 103.67 Mean of 3 days after end of treatment rTMS: 58.59 Sham: 100.64 <i>P</i> < 0.05</p>

AMI = Autobiographical Memory Interview; COWA = Controlled Oral Word Association; MMSE = mini-mental state examination; RAVLT = Rey Auditory Verbal Learning Test; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; WAIS-R = Wechsler Adult Intelligence Scale-Revised

MDD/Bipolar mix

There were no eligible studies.

Tier 3

In MDD-only and MDD/bipolar populations there were no eligible studies.

Key Question 4b: Specific Adverse Events—Overview

This part of KQ 4 concerns specific adverse events from one of the procedural interventions recorded using a systematic method. Results are presented for good- or fair-quality studies.

Overall, 8 studies (16 articles) presented in Table 51^{61-64,77,83,87-89,98,99,115,116,119,124,125} assessed adverse events during acute phase treatment using a systematic method of which only 3 studies (4 articles) found any significant differences in adverse events.^{77,88,89,99}

Table 51. Number of good- and fair-quality studies by TRD tier and diagnostic mix that measure adverse events systematically for KQ 4b

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 3: Probable	0	1 additional
ECT vs. ECT+rTMS	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	1	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2 additional	2 additional
VNS vs. sham	Tier 1: ≥ 2 treatment failures	0	1

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Strength of Evidence: Tier 1 (TRD)

Table 52 documents the strength of evidence concerning specific adverse events in both disease categories combined, limited to Tier 1 studies. It included three comparisons, one of ECT versus ECT plus rTMS,⁶⁴ another study (two articles) that compares rTMS to sham^{77,99} and one that compares VNS to sham.⁹⁸ The comparison of ECT with ECT plus rTMS found no differences. These studies provide low strength of evidence that both rTMS and VNS compared to sham lead to a greater incidence of adverse events. This low strength of evidence is subject to change with the addition of more studies.

One RCT comparing VNS with sham provided low strength of evidence that there were no significant differences overall in the systematic assessment of specific adverse events, although the reporting of particular events appears to be numerically higher in the VNS group.

Key Question 4b: Specific Adverse Events—Key Points

Evidence on adverse events is very limited; only 8 studies (16 articles)^{61-64,77,83,87-89,98,99,115,116,119,124,125} reported specific adverse events using a systematic method; 4 of these found some differences in adverse events.^{77,88,89,98,99} This section does not include studies assessing cognitive function; those are addressed in KQ 4a. The single good-quality RCT, a head-to-head comparison of ECT versus rTMS, did not report any significant differences in specific adverse events.⁶¹⁻⁶³ Five of the studies compared rTMS versus sham procedures; of these, one used escitalopram (20 mg) in both groups. These five studies provide some evidence that rTMS results in more scalp pain and discomfort at the stimulation site, toothache, and muscle twitching than sham, but that there is no difference in headaches or seizures and the adverse effects tend to fade rapidly.

Table 52. Strength of Evidence: specific adverse events – Tier 1

Comparison	Number of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. ECT plus rTMS	1; 22	High 1 RCT Fair	Unknown, single study	Indirect	Imprecise	No significant differences in specific adverse events Low
rTMS vs. sham	1; 68	High 1 RCT Good	Unknown, single study (as most of the specific adverse events were assessed by a single study)	Indirect	Imprecise	Some evidence suggests no significant differences in specific adverse events, while some evidence suggests that rTMS results in more scalp pain at the stimulation site Low
VNS vs. sham	1; 235	Medium 1 RCT Fair	Unknown, single study	Indirect	Imprecise	Some differences in specific adverse events reported but $P = NR$ Low

CBT = cognitive behavioral; ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation, VSN = vagus nerve stimulation

One RCT comparing VNS with sham did not test the statistical significance of differences in specific adverse events. This study did report an increased frequency of particular events with VNS treatment—including voice alteration, cough, dyspnea, dysphasia, and neck pain.

Key Question 4b: Specific Adverse Events—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

There were no eligible studies in Tier 1 or 2. In Tier 3 there were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies in an MDD-only population and one study (three articles) in an MDD/bipolar mix population.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Table 53 shows one head-to-head RCT that compared ECT (n = 24) with rTMS (n = 22) and did not report any significant differences in specific adverse events.⁶¹⁻⁶³ The study used the Columbia ECT Subjective Side Effects Schedule, modified to include potential rTMS side effects (e.g., seizure induction, scalp discomfort, hearing loss) and any unpredictable side effects. The study reported that the ECT group had lower overall scores for subjective side effect symptoms at the end of treatment ($P = 0.02$), but did not find differences in the group by time interaction analysis ($P = 0.49$). The study did not report frequency of each specific side effects. Additionally there was one death in the rTMS arm; however, it was unrelated to treatment.

Table 53. Adverse events assessed systematically of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome Scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
McLoughlin et al., 2007, ⁶¹ Eranti et al., 2007, ⁶² and Knapp et al., 2008 ⁶³ RCT ECT CSSES modified Good	ECT (n = 24) 82% bilateral, mean session 6.3 (2.5) rTMS (n = 22) High frequency, 15 sessions	CSSES Baseline mean (SD) ECT: 14.2 (4.7) rTMS 13.2 (5.8) End of Treatment ECT: 6.7 (6.4) rTMS: 9.7 (4.6) At 6 months ECT: 7.1 (4.7) rTMS: 8.9 (4.7) Group effect $P = 0.02$ Group by time interaction, $P = 0.49$ No treatment-related major adverse events recorded during study (i.e., seizure induction, anesthetic complications, mania)

CSSES = Columbia Subjective Side Effects Schedule; ECT = electroconvulsive therapy; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

There were no eligible studies in Tier 2 or 3. In Tier 1, there was one eligible study in an MDD-only population and zero studies in an MDD/bipolar mix population.

Tier 1

There one study in an MDD-only population and no studies in an MDD/bipolar mix population.

Table 54 shows one study that compares ECT in 11 patients to ECT plus rTMS in another 11 patients.⁶⁴ The ECT-only arm had more side effects numerically ($P = \text{NR}$) than the mixed arm, while differences between groups on specific side effects were not significant. The authors attribute the difference to the reduction in ECT treatments in the mixed group that had some rTMS instead of ECT.

Table 54. Adverse events assessed systematically of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Design Outcome Scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Pridmore et al., 2000 ⁶⁴ RCT A six-item self-report side-effects questionnaire Fair	ECT (n = 11) 100% unilateral, 6 sessions ECT plus rTMS (n = 11) ECT: 100% unilateral (day 1), plus high frequency rTMS: (days 2-5) Repeated in week 2	Positive side-effects questionnaire score ECT: 56 ECT plus rTMS: 31. <i>P</i> = NR Patients reporting side effects at week 2 Headache ECT: 9 ECT plus rTMS: 6 Muscle Pains ECT: 6 ECT plus rTMS: 4 Breathing problems, other pains, other problems (Data NR) For all comparisons, <i>P</i> = NS

CCSES = Columbia Subjective Side Effects Schedule; ECT = electroconvulsive therapy; NR = not reported; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1 consists of one RCT in patients with a diagnosis of MDD and no studies in patients with a mixed diagnosis of MDD/bipolar. In Tier 2 there were no eligible studies in the MDD-only population and two RCTs in an MDD/bipolar population. Within Tier 3, no eligible studies were identified.

Tier 1

There was one RCT in patients with a diagnosis of MDD and no studies in patients with a mixed diagnosis of MDD/bipolar.

MDD-Only

One RCT (N = 68) comparing high-frequency rTMS to sham used the SAFTEE (Systematic Assessment for Treatment Emergent Effects) instrument to measure adverse events, as seen in Table 55.^{77,99} The results showed no significant differences between rTMS and sham. Additionally it was reported that zero seizures occurred in subjects in both groups. However, the rTMS group experienced more occasions of scalp pain at the stimulation site at session one (41 percent) and session 15 (33 percent) than the sham group (0 and 3 percent, respectively).

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were two studies in the MDD-only population and two RCTs in an MDD/bipolar population.

Table 55. Adverse events assessed systematically of rTMS versus sham: Tier 1, MDD

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Avery et al., 2006 ^{77,99} RCT SAFTEE Scores Good	rTMS (n = 35) High frequency, 15 sessions over 4 weeks Sham (n = 33)	SAFTEE Scores Scalp pain at the stimulation site,% Session 1: rTMS: 41 vs. sham: 0, $P < 0.05$ Session 15: rTMS: 33 vs. sham: 3, $P < 0.05$ Seizures, n: rTMS: 0 vs. sham: 0 Changes in SAFTEE (from baseline in 128 individual scores for any emerging symptoms that suggest adverse effects): rTMS vs. sham $P = NS$ (Data = NR)

N = number; NS = not significant; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SAFTEE = Systematic Assessment for Treatment Emergent Effects

MDD-Only

Table 56 contains the two studies that compare rTMS to sham.^{83,87,115,116,119,124,125} The first study used a modification of the Medical Dictionary for Regulatory Activities (MedRA) to code spontaneously reported adverse events. Adverse events recorded include headache, discomfort at stimulation site, insomnia, worsening of depression or anxiety, gastrointestinal, fatigue, muscle aches, vertigo, facial muscle twitching, and other. There were no statistical differences between rTMS and sham in the adverse events recorded.

The second study, as seen in Table 56, also used MedRA to record spontaneously reported adverse events. The following events occurred at a rate greater than 5 percent and occurred at least twice as much in the rTMS patients than sham: eye pain, toothache, application site discomfort, application site pain, facial pain, muscle twitching, and pain of skin. There were no statistical differences reported ($P = NR$).

MDD/Bipolar mix

Table 57 shows the two studies that compare rTMS to sham in Tier 2 patients diagnosed with MDD and bipolar disorder. One RCT reported no difference in trouble concentrating between rTMS and sham groups.⁸⁸ This study also compared adverse events using a multiple-symptom “Side Effect Checklist.” Adverse events recorded include poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appetite, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor coordination, and muscle stiffness. Only one adverse event showed a significant difference between comparisons. “Difficulty starting urination” was reported significantly more often among the rTMS patients (2.0 vs. 1.1, $P = 0.03$) (Table 57).⁸⁸

Table 56. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events
George et al., 2010 ⁸³ RCT MedRA used Good	rTMS (n = 92) High frequency, 15 sessions Sham (n = 98)	Med RA Headache, discomfort at stimulation site, insomnia, worsening of depression or anxiety, gastrointestinal, fatigue, muscle aches, vertigo, facial muscle twitching, and other: No significant difference
O'Reardon et al., 2007, ⁸⁷ Janicak, 2007*, ¹¹⁵ Solvason et al., 2007, ¹¹⁶ Janicak et al., 2010; ¹¹⁹ Demitrack et al., 2008 ¹²⁴ Janicak et al., 2008 ¹²⁵ RCT MedRA used Fair	rTMS (n = 165) High frequency, 20-30 sessions Sham (n = 160)	MedRA Exacerbation of depression, % rTMS:0.6 vs. sham:1.9 Eye pain, % rTMS: 6.1 vs. sham: 1.9 GI disorders toothache, % rTMS: 7.3 vs. sham: 0.6 Application site discomfort, % rTMS: 10.9 vs. sham: 1.3 Application site pain, % rTMS: 35.8 vs. sham: 3.8 Facial pain, % rTMS: 6.7 vs. sham: 3.2 Muscle twitching, % rTMS: 20.6 vs. sham: 3.2 Pain of skin, % rTMS: 8.5 vs. sham: 0.6] <i>P</i> = NR

GI = gastrointestinal; MedRA = Medical Dictionary for Regulatory Activities; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus
*This study came from an unpublished source (conference proceeding).

Table 57. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Berman et al., 2000 ⁸⁸ RCT SECL Fair	rTMS (n = 10) High frequency, 10 sessions Sham (n = 10)	SECL Headache, %: rTMS: 60 vs. sham: 50 <i>P</i> = NR Difficulty starting urination (ordinal scores from 0, none at all, to 3, severe): rTMS: 2.0 vs. sham: 1.1 <i>P</i> = 0.03 No significant difference between groups after correction for multiple comparisons (data NR)

Table 57. Adverse events assessed systematically of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder (continued)

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Bretlau et al., 2008 ⁸⁹ RCT UKU side effect scale Fair	rTMS (n = 25) High frequency, 15 sessions over 3 weeks Sham (n = 24) Both groups received 20 mg escitalopram	UKU side effect scale, mean scores Concentration difficulties: At week 3 rTMS: 1.43 vs. sham: 1.52 At week 12 rTMS: 0.71 vs. sham: 1.22 $P < 0.05$ Tension/inner unrest, tremor, akathisia, nausea, diarrhea, sweating, diminished sexual desire, headache, memory impairment, dry mouth, palpitations, and micturia: No significant difference between groups

mg = milligram; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SECL = Side Effect Checklist; UKU = Udvaig for Kliniske Undersogslser; vs. = versus

The other Tier 2 RCT (N = 49) compared rTMS with sham along with escitalopram (20 mg) in both groups and used the Udvaig for Kliniske Undersogslser (UKU) side-effect scale to assess side effects.⁸⁹ Among the specific side effects assessed, they found no significant difference in headaches between groups. At 12-week followup, significantly more patients in the sham procedure group had difficulties concentrating than did rTMS patients (1.22 versus 0.71 on 0 to 3 scale, $P < 0.05$).

Tier 3

There were no eligible studies.

Vagus Nerve Stimulation Versus Sham

There were no eligible studies in an MDD-only population and one study in an MDD/bipolar population in Tier 1. There were no eligible studies in Tiers 2 or 3.

Tier 1

There were no eligible studies in an MDD-only population and one study in an MDD/bipolar population.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Table 58 shows a Tier 1 RCT (N = 235) that compared VNS versus sham.⁹⁸ The study used the COSTART (Coding Symbols for Thesaurus of Adverse Reaction Terms) dictionary to assess adverse events. Many adverse events were listed, but no statistical analysis was conducted in the article. Numerous adverse events were more commonly reported in the VNS group than the sham group ($P = \text{NR}$). These included voice alteration (68% vs. 38%), cough increased (29% vs. 9%), dyspnea (23% vs. 14%), dysphasia (21% vs. 11%), and neck pain (21% vs. 10%) (for all P

= NR). One participant underwent device explantation due to infection. Eleven patients (4 in VNS group and 7 in sham group) had worsening depression requiring hospitalization.

Table 58. Adverse events assessed systematically of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Outcome scale Quality	Intervention and Sample Size Study Details	Adverse Events (Pain, Concentration, Sleep)
Rush et al., 2005 ⁹⁸ RCT COSTART dictionary. Fair	VNS (n = 119) 10 weeks of VNS therapy with continued medications Sham (n = 116)	COSTART Dictionary (VNS vs sham)* Voice alteration (68% vs. 38%) Cough increased (29% vs. 9%) Dyspepna (23% vs. 14%) Dysphasia (21% vs. 11%) Neck pain (21% vs. 10%) Paresthesia (16% vs. 10%) Vomiting (11% vs. 5%) Laryngismus (11% vs. 2%) Dyspepsia (10% vs. 5%) Wound Infection (8% vs. 2%) Palpitations (8% vs. 2%) *article reports only AEs VNS ≥ 1.5 frequency of sham For all specific adverse events, P = NR Overall serious adverse events, n: VNS: 16 vs. sham: 14 (12 events in 11 patients [VNS: 4, sham: 7] were cases of worsening depression requiring hospitalization)

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; VNS = vagus nerve stimulation

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Key Question 4c: Tolerability as Measured by Withdrawals due to Adverse Events—Overview

Withdrawals due to an adverse event illustrate the general tolerability of treatments for TRD. People who cannot tolerate the adverse effects of the treatments fall into this category. Overall, reporting of withdrawals due to adverse events was limited for some comparisons by the fact that no statistical significance was reported by the authors when withdrawals occurred.

Overall, 21 studies reported withdrawals due to adverse events (Table 59). When considering only studies conducted in TRD (Tier 1) MDD-only patients, we identified one head-to-head trial of ECT versus rTMS¹²³ and four rTMS versus sham studies (five articles).^{69,71,76,77,99} In a Tier 1 MDD/bipolar population, we identified four studies that compared rTMS to sham^{18,74,80,81} and one study that compared VNS to sham.⁹⁸

Table 59. Number of good- and fair-quality studies by TRD tier and diagnostic mix that assess withdrawals due to adverse events for KQ 4c

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	1	0
ECT vs. rTMS	Tier 3: Probable	0	2 additional
ECT vs. sham	Tier 3: Probable	0	1 additional
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	4	4
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	3 additional	0
rTMS vs. sham	Tier 3: Probable	0	2 additional
VNS vs. sham	Tier 1: ≥ 2 treatment failures	0	1
CBT vs. usual care	Tier 2: ≥ 1 treatment failure	1 additional	2 additional

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; MDD = major depressive disorder; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Additional eligible studies were found in Tiers 2 and 3. Three studies (8 articles) were conducted in Tier 2 patients with MDD comparing rTMS to sham.^{83,86,87,115,116,119,124,125} Two Tier 3 studies comparing rTMS versus sham in an MDD/bipolar mix population were identified.^{90,91} One Tier 2 study in patients with MDD⁹⁴ and two Tier 2 studies in patients with an MDD/bipolar mix (three articles) compared CBT versus usual care.^{93,95,96} Two head-to-head studies (four articles) in Tier 3 compared ECT with rTMS^{61-63,126} and one study compared ECT to sham⁶⁸ in a population diagnosed with MDD and bipolar disorder.

Strength of Evidence: Tier 1 (TRD)

Few studies provide relevant data (Table 60). One small study showed no differences in withdrawals in ECT versus rTMS (statistical significance not reported), leading to a grade of low strength of evidence that withdrawals due to adverse events were greater with ECT than rTMS. In the rTMS versus sham group the results are mixed, with the data not providing a clear direction of effect of the treatment on withdrawals due to adverse events, resulting in a strength grade of insufficient. There was low strength of evidence that there were greater withdrawals due to adverse events in the vagus nerve stimulation group compared to sham.

Table 60. Strength of evidence: withdrawals due to adverse events -- Tier 1

Comparison	Number Of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. rTMS	1; 30	Medium 1 fair prospective cohort study	Unknown	Direct	Imprecise	No differences between groups in ECT vs. rTMS P = NR Low
rTMS vs. sham	7; 277	Medium 7 RCTs 1 good, 6 fair	Inconsistent	Indirect	Imprecise	Mixed results Insufficient
VNS vs. sham	1; 235	Low RCT Good	Unknown	Indirect	Precise	More withdrawals due to AEs in the VNS group P = NR Low

AE = adverse event; ECT = electroconvulsive therapy; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Key Points

Withdrawals due to adverse events illustrate the general tolerability of treatments for treatment-resistant depression. Overall, reporting of withdrawals due to adverse events was limited by the fact that no tests of statistical significance were performed by the authors when withdrawals occurred.

Key Question 4c: Tolerability as Measured by Withdrawals Due to Adverse Events—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1 consists of one prospective cohort study in an MDD population and none in an MDD/bipolar population (Table 61). Tier 2 has no eligible studies. Tier 3 has no studies in MDD-only patients and two RCTs in MDD/bipolar mix patients.

Tier 1

There was one prospective cohort study in an MDD population and none in an MDD/bipolar population.

MDD-Only

One fair-quality prospective cohort study¹²³ adequately reported withdrawals due to adverse events. This observational study reported greater withdrawals in the ECT versus rTMS group (7.1% versus 0%, respectively).¹²³ Sample sizes were small, all with less than 20 patients per study arm (Table 61).

Table 61. Withdrawals due to adverse events of ECT versus rTMS: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Schulze-Rauschenbach et al., 2005 ¹²³ Prospective cohort 1 week (post-test measurement 8.8 days after txt) Fair	ECT (n = 14) Right unilateral txt for 2 weeks rTMS (n = 16) High frequency, mean 10.8 sessions (SD 1.4)	Due to AEs, n (%): ECT: 1 (7.1) rTMS: 0 (0) P = NR

AE = adverse event; ECT = electroconvulsive therapy; NR = not reported; P = p-value; SD = standard deviation; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and two RCTs in MDD/bipolar mix patients.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two RCTs (four articles, one good-quality and one fair-quality).^{61-63,126} They reported no withdrawals due to adverse events (Table 62).

Table 62. Withdrawals due to adverse events of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
McLoughlin et al., 2007, ⁶¹ Eranti et al., 2007, ⁶² and Knapp et al., 2008 ⁶³ RCT 3 weeks Good	ECT (n = 24) 82% bilateral, mean sessions 6.3 (SD 2.5) rTMS (n = 22) High frequency, 15 sessions	Due to AEs: 0
O'Connor, 2003 ¹²⁶ Prospective cohort Up to 4 weeks Fair	ECT (n = 14) Unilateral, 3 times per week for 2 to 4 weeks rTMS (n = 14) High frequency, 10 sessions	Due to AEs: 0

AE = adverse event; ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Electroconvulsive Therapy Versus Sham

Tier 1 has no eligible studies (Table 63). Tier 2 has no eligible studies. Tier 3 has no studies in MDD-only patients and one RCT in MDD/bipolar mix patients.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and one RCT in MDD/bipolar mix patients (Table 63).

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One study in a population with “severe endogenous depression” referred for ECT.⁶⁸ Withdrawals due to adverse events were 5.7 percent in the ECT arm and 0 in the simulated ECT arm (see Table 63).

Table 63. Withdrawals due to adverse events of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Johnstone et al., 1980 ⁶⁸ RCT 3 weeks Fair	ECT (n = 35) Bilateral, 8 sessions Sham (n = 35)	Due to AEs (%): ECT: 5.7 Sham: 0 P = NR

AE = adverse event; ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1 contains four RCTs in patients with MDD-only (Table 64) and three RCTs in MDD/bipolar patients (Table 65). There are three RCTs in an MDD-only population and no

Table 64. Withdrawals due to adverse events of rTMS versus sham: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Avery et al., 2006 ⁷⁷ and Avery et al., 2007 ⁹⁹ RCT 4 weeks Good	rTMS (n = 35) High frequency, 15 sessions Sham (n = 33)	Due to AEs: 0
Boutros, et al., 2002 ⁶⁹ RCT 2 weeks Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 9)	Due to AEs: 0
Garcia-Toro et al., 2006 ⁷¹ RCT 2 weeks Fair	rTMS-1 (n = 10) High frequency plus low frequency, 10 sessions rTMS-2 (n = 10) Same as above with individually assessed location Sham: (n = 10)	Due to AEs: 0
Holtzheimer et al., 2004 ⁶⁶ RCT 2 weeks Fair	rTMS (n = 7) High frequency, 10 sessions Sham (n = 8)	Due to AEs: 0

AE = adverse event; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Table 65. Withdrawals due to adverse events of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Fitzgerald et al., 2006 ¹⁸ RCT 6 weeks Fair	High plus low rTMS (n = 25) High-frequency rTMS up to 30 sessions plus low-frequency rTMS up to 30 sessions Sham (n = 25)	Due to AEs: 0
Fitzgerald et al., 2003 ⁸⁰ RCT Phase I: 2 weeks Fair	High rTMS (n = 20) High frequency, 10 sessions Low rTMS (n = 20) Low frequency, 10 sessions Sham (n = 20)	Due to AEs: 0
Pallanti et al., 2010{#2551} RCT 3 weeks Fair	Low plus High rTMS (n = 20) Low then high frequency, 15 sessions rTMS (n = 20) Low frequency, 15 sessions Sham (n = 20)	Due to AEs, n (%): Low plus high rTMS: 0 (0) Low rTMS: 0 (0) Sham: 0 (0) P = NR
Su et al., 2005 ⁸¹ RCT 2 weeks Fair	20 Hz rTMS (n = 11) High frequency (20 Hz), 10 sessions 5 Hz rTMS (n = 11) High frequency (5 Hz), 10 sessions Sham (n = 11)	Due to AEs, %: All rTMS: 9.1 20 Hz rTMS: 0 5 Hz rTMS: 17 Sham: 0 P = NR

AE = adverse event; Hz = hertz; n = number; RCT = randomized controlled trial, rTMS = repetitive transcranial magnetic stimulation

eligible studies in MDD/bipolar diagnosis patients in Tier 2. In Tier 3 there were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis.

Tier 1

There are three RCTs in patients with MDD-only and four RCTs in MDD/bipolar patients.

MDD-Only

Table 64 presents one good and three fair RCTs that reported no withdrawals in either patients treated with rTMS or sham.^{69,71,76,77,99}

MDD/Bipolar mix

Four fair RCTs reported withdrawals due to adverse events in patients previously treated two or more times for depression, as seen in Table 65. Three of the studies showed no withdrawals due to adverse events.^{18,74,80} There was one study that showed a difference in withdrawals due to adverse events (rTMS 9.1% versus none for sham).⁸¹ There are important differences between this study and the others in this group, primarily in the strength of the intervention. As can be seen, the RCT that showed differences in withdrawals due to adverse events used more pulses per session, 1,600 versus 750 to 1,000 and 20 Hz versus 10 Hz, which could explain the differences in withdrawals due to adverse events within this group.

Tier 2

There are three RCTs in an MDD-only population and no eligible studies in MDD/bipolar diagnosis patients (Table 66).

Table 66. Withdrawals due to adverse events of rTMS versus sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
George et al., 2010 ⁸³ RCT 3 weeks of txt Good	rTMS (n = 92) High frequency, 15 sessions Sham (n = 98)	Due to AEs, %: rTMS: 5.4 Sham: 0 P = NR
O'Reardon, 2007, ⁸⁷ Janicak, 2007 ¹¹⁵ and Solvason, 2007 ¹¹⁶ Janciak et al., 2008 ¹²⁵ and Janicak et al., 2010 ¹¹⁹ RCT 4 weeks primary endpoint Fair	rTMS (n = 165) High frequency, 20-30 sessions Sham (n = 160)	Due to AEs, %: rTMS: 4.2 Sham: 3.4 P = NR
Stern et al., 2007 ⁸⁶ RCT 2 weeks of txt Fair	High rTMS (n = 10) High frequency, 10 sessions Low-left rTMS (n = 10) Low frequency (Left-DLPFC), 10 sessions Low rTMS (n = 10) Low frequency, 10 sessions Sham (n = 15)	Due to AEs, %: High rTMS: 0 Low-left rTMS: 50 Low rTMS: 0 Sham: 20 P = NR

AE = adverse event; DLPFC = dorsolateral prefrontal cortex; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD-Only

One relatively large (n = 325) study compared Tier 2 patients in an MDD-only population.^{87,115,116,119,124,125} The withdrawals due to adverse events were similar in the rTMS group (4.2%) versus sham (3.4%) over the 4-week time period. Another decent size study (N = 190) compared withdrawals due to adverse events between rTMS at 5.4 percent to sham at 0 percent.⁸³ Additionally a small study (n = 45) compared withdrawals due to adverse events in four arms, high rTMS (n = 10), low-left rTMS (n = 10), low rTMS (n = 10) and sham (n = 15).⁸⁶ Two arms had no withdrawals but the low-left rTMS had 50 percent withdrawals due to adverse event rate and 30 percent in the sham group.

MDD/Bipolar mix

There were no eligible studies.

Tier 3

There were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis (Table 67).

Table 67. Withdrawals due to adverse events of rTMS versus sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Bortolomasi et al., 2006 ⁹⁰ RCT 1 week Fair	rTMS (n = 12) High frequency, 5 sessions Sham (n = 7)	Due to AEs: 0
George et al., 1997 ⁹¹ RCT, crossover Primary endpoint after 2 weeks of txt Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 12)	Due to AEs: 0

AE = adverse event; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

There were two small studies (n = 19 and 24) in a Tier 3 MDD/bipolar mix population comparing rTMS to sham.^{90,91} Neither had any withdrawals due to adverse events.

Vagus Nerve Stimulation Versus Sham

There were no eligible studies in patients with MDD-only and one RCT in patients with an MDD/bipolar diagnosis in Tier 1. In Tiers 2 and 3, there were no eligible studies.

Tier 1

There were no eligible studies in patients with MDD-only and one RCT in patients with an MDD/bipolar mix diagnosis (Table 68).

Table 68. Withdrawals due to adverse events of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Rush et al., 2005 ⁹⁸ , RCT 10 weeks Good	VNS (n = 112) 10 weeks of VNS therapy with continued medications Sham (n = 110)	Due to AEs, %: VNS: 2.7 Sham: 0 P = NR

AE = adverse event; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; VNS = vagus nerve stimulation

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

One good-quality RCT (N = 222) comparing VNS to sham-control in a Tier 1 population reported 2.7 percent withdrawals due to adverse events in the VNS group compared with none in the sham-control group over a 10-week treatment period.⁹⁸

Tier 2

There were no eligible studies.

Tier 3

There were no eligible studies.

Cognitive Behavioral Therapy Versus Usual Care

There were no eligible studies in Tier 1. In an MDD population there was one eligible study and 2 studies in an MDD/bipolar mix population in Tier 2. There were no eligible studies in Tier 3.

Tier 1

There were no eligible studies.

Tier 2

There was one study in MDD-only and 2 studies in patients with an MDD/bipolar mix.

MDD-Only

One RCT reported withdrawals due to adverse events in 491 patients randomized to either medication alone or medication plus psychotherapy over 12 weeks of treatment (Table 69).⁹⁴ The medication-alone arm had 2.1 percent versus 0.8 percent withdrawals in the medication plus psychotherapy due to adverse events.

Table 69. Withdrawals due to adverse events of CBT versus sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Kocsis et al., 2009 ⁹⁴ RCT 12 weeks Fair	CBT plus medication (n =395) Cognitive behavioral analysis system of psychotherapy (n = 200) 16-20 sessions; brief supportive psychotherapy (n = 195) 16-20 sessions Medication only (n=96)	Due to AEs: CBT plus medication: 3 (0.8%) Medication only: 2 (2.1%) P = NR

AE = adverse event; CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

MDD/Bipolar mix

Two RCTs (four articles, one good-quality, one fair-quality) comparing CBT to some form of usual care reported no withdrawals due to adverse events, as shown in Table 70.^{93,95,96,120} These studies ranged in duration from 16 weeks of treatment to 12-month followup periods.

Tier 3

There were no eligible studies.

Table 70. Withdrawals due to adverse events of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Harley, 2008 ⁹³ RCT 16 weeks Fair	CBT ([DBT] (n = 13) 16-sessions of dialectical behavior therapy skill training Control (n = 11) Waitlist	Due to AEs: 0
Paykel, 1999, ⁹⁵ Scott, 2000, ⁹⁶ and Scott, 2003 ¹²⁰ RCT 20 weeks Good	Cognitive Therapy (n = 80) 16 sessions of cognitive therapy plus clinical management Clinical Management (n = 78) Clinical management – patients visited psychiatrist every 4 weeks and continued on current medication	Due to AEs: 0

AE = adverse event; CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

Key Question 4d: Adherence as Measured by Overall Withdrawals—Overview

Of 64 included studies, two studies reporting compliance indicated a 100 percent rate^{66,71} and 1 reported a 63 percent adherence rate.⁸³ Overall withdrawals were used as a proxy to capture compliance as it was recorded more frequently. Out of the 64 included studies, 26 studies (32 articles) reported total withdrawals (for any reason) during treatment (Table 71).

Table 71. Number of good- and fair-quality studies by TRD tier and diagnostic mix that assess overall withdrawals for KQ 4d

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 1: ≥ 2 treatment failures	2	0
ECT vs. rTMS	Tier 3: Probable	0	3 additional
ECT vs. sham	Tier 3: Probable	1 additional	1 additional
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	4	3
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	3 additional	2 additional
rTMS vs. sham	Tier 3: Probable	0	2 additional
CBT vs. usual care	Tier 2: ≥ 1 treatment failure	2 additional	2 additional

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

When considering only studies conducted in Tier 1 patients with MDD, there were two head-to-head trials of ECT versus rTMS^{58,123} and three rTMS versus sham studies (four articles).^{71,76,77,99} There were five Tier 1 studies, conducted in an MDD/bipolar population that compared rTMS to sham.^{18,69,80-82}

Additional eligible studies were found in Tiers 2 and 3. In Tier 2 MDD-only populations, we identified three studies (eight articles) comparing rTMS to sham^{83,86,87,115,116,119,124,125} and two studies in an MDD/bipolar mix population.^{88,89} We also identified two studies in MDD-only populations comparing CBT to usual care.^{94,102} In Tier 2 MDD/bipolar mix populations, we identified two studies (three articles) comparing CBT versus usual care.^{93,95,96} Three head-to-

head studies (four articles) in Tier 3 compared ECT with rTMS in a population diagnosed with MDD and bipolar disorder.^{60-63,126} There are two Tier 3 studies that compared ECT to sham, one in an MDD-only group⁶⁷ and one in an MDD and bipolar population.⁶⁸ There are also two Tier 3 studies that compared rTMS to sham in a MDD and bipolar population.^{90,91}

Strength of Evidence: Tier 1 (TRD)

The data addressing overall withdrawals (Table 72) for ECT versus rTMS showed greater withdrawals in ECT when compared with rTMS ($P = NR$). For rTMS versus sham, mixed results were found. Strength of evidence is low for ECT versus rTMS and insufficient for rTMS versus sham.

Table 72. Strength of evidence: overall withdrawals during treatment -- Tier 1

Comparison	Number Of Studies; Subjects	Risk of Bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. rTMS	2; 72	Medium 1 fair RCT 1 fair prospective cohort study	Consistent	Direct	Imprecise	ECT group had higher number of withdrawals $P = NR$ Low
rTMS vs. sham	8; 325	Medium 8 RCTs 1 good 7 fair	Inconsistent	Indirect	Imprecise	Mixed results Insufficient

ECT = electroconvulsive therapy; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

Key Question 4d: Adherence as Measured by Overall Withdrawals—Key Points

Of the 27 studies with relevant data, there were only three studies (three articles) that assessed adherence or compliance during treatment.^{66,71,83} Two reported that all patients completed all required treatments as specified in the protocol and one reported an overall adherence rate of 62 to 64 percent. As a proxy to explore adherence, we chose overall withdrawals, which are found in 10 Tier 1 studies and an additional 15 studies in Tiers 2 and 3.

Overall, reporting of withdrawals during treatment was limited by the fact that statistical significance was not reported. Studies were generally small and unlikely to have had power to show statistical or clinical significance, methods varied, and there was significant heterogeneity across the populations studied.

Key Question 4d: Adherence as Measured by Overall Withdrawals—Detailed Analysis

As shown in Table 73, there were only three studies that reported adherence or compliance.^{66,71,83} Two of them reported 100 percent compliance and one reported adherence of 62 to 64 percent.

Table 73. Adherence/compliance for all comparable interventions: all tiers

Author, Year Design Duration Tier Quality	Intervention and Sample Size Study Details	Results
Folkerts et al. ⁶⁶ RCT: patient status NR 4 weeks Tier 1 Fair	ECT (n = 21) Right unilateral, mean txts = 7.2 sessions (2-3 weeks) Pharmacotherapy (n = 18) Paroxetine 40 mg (max 50 mg/d, mean daily dosage 44 mg/day	All patients continued their respective therapies through scheduled end of treatment phase
Garcia-Toro et al., 2006 ⁷¹ RCT: outpatient 2 weeks Tier 1 Fair	rTMS-1 (n = 10) High frequency plus low frequency, 10 sessions rTMS-2 (n = 10) Same as above but with individually assessed location Sham: (n = 10)	All completed 10 rTMS sessions
George et al., 2010 ⁸³ RCT Tier 2 Good	rTMS (n = 92) High frequency, 15 sessions Sham (n = 98)	Fully adherent to treatment, % rTMS: 62 Sham: 64

ECT = electroconvulsive therapy; mg/day = milligram per day; n = number; NR = not reported; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

There were two studies, an RCT and a prospective cohort study, in Tier 1. There were no eligible studies in Tier 2; in Tier 3 there were no MDD studies, and in an MDD/bipolar mix there were two RCTs and one prospective cohort study.

Tier 1

There were two studies, an RCT and a prospective cohort study.

MDD-Only

There are two Tier 1 studies that compared ECT to rTMS and reported overall withdrawals, as seen in Table 74. The first is a small RCT (n = 42) that resulted in more withdrawals in the ECT group of 15.1 percent than the rTMS group at 9.1 percent ($P = \text{NR}$).⁵⁸ The second study was a small prospective cohort study (N = 30).¹²³ Similar to the RCT, it showed that the ECT group experienced higher overall withdrawals of 7.1 percent versus 0 percent in the rTMS group, but significance is not reported.

Table 74. Overall withdrawals of ECT versus rTMS: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Rosa et al., 2006 ⁵⁸ RCT Up to 4 weeks Fair	ECT (n = 20) % bilateral NR, mean sessions: 10 (SD 1.5) rTMS (n = 22) High frequency, 10-20 sessions (2-4 weeks)	Overall, %: ECT: 15.0 rTMS: 9.1 P = NR
Schulze-Rauschenbach et al., 2005 ¹²³ Prospective cohort 1 week (post-test measurement 8.8 days after txt) Fair	ECT (n = 14) Right unilateral treatment for 2 weeks, mean # sessions 9.9 (SD 2.7) rTMS (n = 16) High frequency, mean sessions: 10.8 (SD 1.4)	Overall, %: ECT: 7.1 rTMS: 0 P = NR

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; txt = treatment

MDD/Bipolar mix

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

There were no MDD studies and in an MDD/bipolar mix there were two RCTs and one prospective cohort study.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

As shown in Table 75, three studies report overall withdrawals in a Tier 3 population comparing ECT to rTMS. A good-rated RCT reported overall withdrawals in the ECT group of 0 percent compared to 25 percent in the rTMS arm ($P = \text{NR}$).⁶¹⁻⁶³ Another RCT reported overall withdrawals in the ECT group of 26.7 percent compared to 33.3 percent in the rTMS arm.⁶⁰ A small prospective cohort reported no overall withdrawals in either arm.¹²⁶

Electroconvulsive Therapy Versus Sham

Tier 1 has no eligible studies (Table 76). Tier 2 has no eligible studies. Tier 3 has one study in MDD-only patients and one RCT in MDD/bipolar mix patients.

Tier 1

There were no eligible studies.

Tier 2

There were no eligible studies.

Tier 3

Two trials comparing ECT with sham stimulation were identified in Tier 3.

MDD-Only

There was one study, in Table 76, in a population with “primary depressive illness” referred for ECT.⁶⁷ Overall withdrawals were recorded as 15.4 percent in the ECT group versus 8.3 percent in the simulated ECT group ($P = \text{NR}$).

Table 75. Overall withdrawals of ECT versus rTMS: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Withdrawals during treatment
McLoughlin et al., 2007, ⁶¹ Eranti et al., 2007, ⁶² and Knapp et al., 2008 ⁶³ RCT 3 weeks Good	ECT (n = 24) 82% bilateral, mean sessions: 6.3 (SD 2.5) rTMS (n = 22) High frequency, 15 sessions	Overall, % ECT: 0 rTMS: 25 $P = \text{NR}$
Hansen, 2010 ⁶⁰ RCT 3 weeks Fair	ECT (n = 30) 100% unilateral, 9 sessions rTMS (n = 30) Low frequency, 15 sessions	Overall, % ECT: 26.7 rTMS: 33.3 $P = \text{NR}$
O'Connor, 2003 ¹²⁶ Prospective cohort Up to 4 weeks Fair	ECT (n = 14) Unilateral, 3 times per week for 2 to 4 weeks rTMS (n = 14) High frequency, 10 sessions	Overall: 0

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Table 76. Withdrawals due to adverse events of ECT versus sham: Tier 3, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
West, 1981 ⁶⁷ RCT Up to 3 weeks Fair	ECT (n = 13) Bilateral, 6 sessions Sham (n = 12)	Overall withdrawals (%): ECT: 15.4 Sham: 8.3 $P = \text{NR}$

ECT = electroconvulsive therapy; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

MDD/Bipolar mix

There was one study, shown in Table 77, in a population with “severe endogenous depression” referred for ECT.⁶⁸ Overall withdrawals were recorded as 11.4 percent in the ECT group and 11.4 percent in the simulated ECT group ($P = \text{NR}$).

Table 77. Withdrawals due to adverse events of ECT versus sham: Tier 3, MDD and and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Discontinuations During Treatment
Johnstone et al., 1980 ⁶⁸ RCT 3 weeks Fair	ECT (n = 35) Bilateral, 8 sessions Sham (n = 35)	Overall withdrawals (%): ECT: 11.4 Simulated ECT: 11.4 P = NR

ECT = electroconvulsive therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation.

Repetitive Magnetic Stimulation Versus Sham

Tier 1 contains four RCTs in patients with MDD-only and three RCTs in MDD/bipolar patients. There are three RCTs in an MDD-only population and two eligible studies in an MDD/bipolar population in Tier 2. In Tier 3 there were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix population.

Tier 1

MDD-Only

There are four RCTs that compare overall withdrawals in rTMS versus sham in a Tier 1 population (see Table 78). Two report that there are no withdrawals in either the rTMS or sham arms.^{71,76} An RCT conducted in 68 patients showed an overall withdrawal rate of 9.1 percent in the rTMS arm and 8.6 percent in the sham arm ($P = NR$).^{77,99} Another RCT of 21 patients had overall withdrawals of 8.3 percent in the rTMS group and 30.0 in the sham group.⁶⁹

Table 78. Overall withdrawals of rTMS to sham: Tier 1, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Avery et al., 2006 ^{77,99} RCT 4 weeks Good	rTMS (n = 35) High frequency, 15 sessions Sham (n = 33)	Overall, %: rTMS: 9.1 Sham: 8.6 P = NR
Boutros, et al., 2002 ⁶⁹ RCT 2 weeks Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 9)	Overall, %: rTMS: 8.3 Sham: 30.0 P = NR
Garcia-Toro et al., 2006 ⁷¹ RCT 2 weeks Fair	rTMS-1 (n = 10) High frequency plus low frequency, 10 sessions rTMS-2 (n = 10) Same as above but with individually assessed location Sham: (n = 10) Double winged coil angled at 45 degrees	Overall: 0
Holtzheimer et al., 2004 ⁷⁶ RCT 2 weeks Fair	rTMS (n = 7) High frequency, 10 sessions Sham (n = 8)	Overall: 0

n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

MDD/Bipolar mix

Four RCTs comprise the MDD/bipolar mix in a Tier 1 population, as shown in Table 79. One RCT conducted in 40 patients had zero withdrawals in any arm.⁸⁰ Another RCT with 48 patients also had zero withdrawals.⁸² Another small study (N = 33) had 9.1 percent overall withdrawals in the rTMS and sham groups.⁸¹ A larger study, 50 patients, had 0 percent overall withdrawals in the rTMS group and 12 percent in the sham group.¹⁸

Table 79. Overall withdrawals of rTMS to sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Fitzgerald et al., 2006 ¹⁸ RCT 6 weeks Fair	High plus Low rTMS (n = 25) High frequency plus low frequency, up to 30 sessions Sham (n = 25)	Overall, %: rTMS: 0 Sham: 12 P = NR
Fitzgerald et al., 2003 ⁸⁰ RCT Phase I: 2 weeks Phase II: NA Fair	High rTMS (n = 20) High frequency, 10 sessions Low rTMS (n = 20) Low frequency, 10 sessions Sham (n = 20)	Overall: 0
Su et al., 2005 ⁸¹ RCT 2 weeks Fair	20 Hz rTMS (n = 11) High frequency (20 Hz), 10 sessions 5 Hz rTMS (n = 11) High frequency (5 Hz), 10 sessions Sham (n = 11)	Overall, % 10 Hz rTMS and 5 Hz rTMS: 9.1 Sham: 9.1 P = NR
Triggs et al., 2010 ⁸² RCT 2 weeks Fair	High rTMS (n = 18) High frequency, 10 sessions High right rTMS (n = 16) High frequency to the right prefrontal cortex, 10 sessions Sham left (n = 7) Sham right (n = 7) NOTE: Patients in all groups also received a social support intervention	Overall: 0

Hz = Hertz; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tier 2

MDD-Only

There were three RCTs in Tier 2 in MDD-only patients, as seen in Table 80. A relatively large study, 325 patients, had overall withdrawals of 13.3 percent in the rTMS arm and 16.3 percent in the sham arm.^{87,115,116,119,124,125} The second study, conducted with 190 patients, had overall withdrawals of 12 percent in the rTMS arm and 9 percent in the sham arm.⁸³ A small study (n = 45) compared overall withdrawals in four arms, high rTMS (n = 10), low-left rTMS (n = 10), low-right rTMS (n = 10), and sham (n = 15). Two arms had no withdrawals but the low-left rTMS had a 20 percent overall withdrawal rate and 6.7 percent in the sham group.⁸⁶

Table 80. Overall withdrawals of rTMS to sham: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
George et al., 2010 ⁸³ RCT Up to 6 weeks of txt Good	rTMS (n = 92) High frequency, 15 sessions Sham (n = 98)	Overall, % rTMS: 12 Sham: 9 P = NR
O'Reardon, 2007 ^{87,115,116,119,124,125} RCT 4 weeks primary endpoint Fair	rTMS (n = 165) High frequency, 20-30 sessions Sham (n = 160)	Overall, % rTMS: 13.3 Sham: 16.3 P = NR
Stern et al., 2007 ⁸⁶ RCT 2 weeks of txt Fair	High rTMS (n = 10) High frequency, 10 sessions Low-left rTMS (n = 10) Low frequency, (1 Hz), Left DLPFC, 10 sessions Low rTMS (n = 10) Low frequency, 10 sessions Sham (n = 15)	Overall: High rTMS: 0 Low-left rTMS: 20 Low rTMS: 0 Sham: 6.7 P = NR

DLPFC = dorsolateral prefrontal cortex; n = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

MDD/Bipolar mix

Table 81 provides the two studies that were found in a Tier 2 MDD/bipolar population.^{88,89} Overall withdrawals were 0 percent in the rTMS arm and 30 percent in the sham arm. However, no significance was reported.⁸⁸ The final study in this group had overall withdrawals of 12.0 percent in the rTMS arm versus 4.2 percent but significance is not reported.⁸⁹

Table 81. Overall withdrawals of rTMS to sham: Tier 2, MDD and and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Berman et al, 2000 ⁸⁸ RCT 2 weeks Fair	rTMS (n = 10) High frequency, 10 sessions Sham (n = 10)	Overall: rTMS: 0 Sham: 30 P = NR
Bretlau et al., 2008 ⁸⁹ RCT 3 weeks Fair	rTMS (n = 25) High frequency, 15 sessions over 3 weeks Sham (n = 24) Both groups received 20 mg escitalopram	Overall, %: rTMS: 12.0 Sham: 4.2 P = NR

mg = milligram; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation

Tier 3

There were no studies in MDD-only patients and two RCTs in patients with an MDD/bipolar mix diagnosis.

MDD-Only

There were no eligible studies.

MDD/Bipolar mix

Two small studies, 19 and 24 patients, compared rTMS and sham in Tier 3 subjects, as seen in Table 82.^{90,91} Neither of these studies had any overall withdrawals.

Table 82. Overall withdrawals of rTMS to sham: Tier 3, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Bortolomasi et al., 2006 ⁹⁰ RCT 1 week Fair	rTMS (n = 12) High frequency, 5 sessions Sham (n = 7)	Overall: 0
George et al., 1997 ⁹¹ RCT, crossover Primary endpoint after 2 weeks of txt Fair	rTMS (n = 12) High frequency, 10 sessions Sham (n = 12)	Overall: 0

N = number; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Cognitive Behavioral Therapy Versus Usual Care

There were no eligible studies in Tier 1. Tier 2 had two studies in patients with MDD-only and two studies in patients diagnosed with MDD/bipolar mix; there were no eligible studies in Tier 3.

Tier 1

There were no eligible studies.

Tier 2

There were two studies in patients with MDD-only and two studies in patients diagnosed with MDD/bipolar mix.

MDD-Only

Table 83 provides two studies, one small study of 32 patients¹⁰² and one larger study of 491 patients,⁹⁴ conducted in MDD-only Tier 2 patients. In the smaller study, the overall withdrawal rate was 16.7 percent in the CBT arm and 42.9 percent in the usual care arm. Statistical significance was not reported; the CBT arm had 26 subjects compared to 6 in the usual care arm. The larger study had overall withdrawals of 16.6 percent in the medication arm and 13.2 percent in the medication plus psychotherapy arm ($P = \text{NR}$).

MDD/Bipolar mix

Two studies (four articles) compared CBT to usual care with mixed results in patients with MDD/bipolar mix in Tier 2 (see Table 84). The smaller one, 24 patients, had an overall withdrawal rate of 23.1 percent in the CBT arm and 18.2 percent in the waitlist control arm.⁹³ A larger study, 158 patients, had overall withdrawals of 15.4 percent in the CBT arm versus 23.8 percent in the usual care arm.^{95,96,120} For either study, statistical significance was not reported.

Table 83. Overall withdrawals of CBT versus medication: Tier 2, MDD

Author, Year Design Duration Quality	Intervention and Sample Size Study Details	Results
Kocsis et al., 2009 ⁹⁴ RCT 12 weeks Fair	CBT plus medication (n =395) Cognitive behavioral analysis system of psychotherapy (n = 200); 16-20 sessions; brief supportive psychotherapy (n = 195) 16-20 sessions Medication only (n=96)	Overall, % CBT plus medication: 13.2 Medication: 16.6 P = NR
Moore et al., 1997 ¹⁰² RCT Active phase occurred during 12-month followup phase Fair	CBT (n = 26) Minimum of 4 treatments in 1st month, 2 treatments in 2nd month, and 1 per month following Medication (n = 6) Continued or new medication dose within recognized therapeutic threshold	Overall, % CBT: 16.7 Medication: 42.9 P = NR

CBT = cognitive behavioral therapy; n = number; NR = not reported; P = p-value; RCT = randomized controlled trial

Table 84. Overall withdrawals of CBT versus usual care: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Design Quality	Intervention and Sample Size Study Details	Results
Harley, 2008 ⁹³ RCT 16 weeks Fair	CBT [DBT] (n = 13) 16-session, once-weekly group covered the 4 dialectical behavior therapy skill sets Control (n = 11) Waitlist	Overall, % CBT: 23.1 Usual care: 18.2 P = NR
Paykel, 1999 ⁹⁵ and Scott, 2000 ⁹⁶ and Scott, 2003 ¹²⁰ RCT 20 weeks Good	CBT (n = 80) 16 cognitive behavioral therapy sessions plus clinical management Clinical Management (n = 78) Clinical management alone – patients visited psychiatrist every 4 weeks and continued on current medication	Overall, % CBT plus clinical management: 15.4 Clinical management: 23.8 P = NR

CBT = cognitive behavioral therapy; n = number; RCT = randomized controlled trial

Tier 3

There were no eligible studies.

Key Question 5: Efficacy and Harms for Selected Populations

Overview

Studies that focused on subgroups or included a subanalysis for a special population were eligible for consideration for this KQ. Most studies were excluded because the subgroup analysis was not comparative between groups, but rather descriptive within an intervention group. Two randomized controlled trials were in specific age populations, one Tier 1 study involving rTMS compared with sham⁷⁵ and one Tier 3 trial of ECT versus sham.^{68,127,128} Three RCTs, one Tier 1 and two Tier 2, focused on post-stroke depression, comparing rTMS to a sham intervention^{129,130} (Table 85).

Table 85. Number of good- and fair-quality studies by TRD tier and diagnostic mix of subpopulations presented in KQ 5

Comparison	Tier	MDD-Only	MDD and Bipolar Disorder
ECT vs. sham	Tier 3: Probable	1	0
rTMS vs. sham	Tier 1: ≥ 2 treatment failures	2	0
rTMS vs. sham	Tier 2: ≥ 1 treatment failure	2	0

ECT, electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation.

Strength of Evidence: Tier 1 (TRD)

Strength of evidence assessment was made for three outcomes: change in depressive severity, response rate, and remission rate for the two Tier 1 trials comparing rTMS versus sham (Table 86). Remission rate was not addressed in the one younger adult age group trial. Strength of evidence is low for each outcome, given that there is only one small study for each subpopulation of interest. No *P* value was reported for the change in depressive severity; in the one age subpopulation trial, however, there was a significant difference favoring rTMS in response rates.

Table 86. Strength of Evidence: Efficacy and other comparative clinical outcomes of rTMS versus sham -- Tier 1, MDD

Comparison	Number of Studies; Subjects	Risk of bias Design/ Quality	Consistency	Directness	Precision	Results and Strength of Evidence
Change in depressive severity	2; 54	Low RCT Fair	Consistent	Indirect	Precise	rTMS > sham in young adult population (ages 18–37) rTMS > sham in older adults with post-stroke depression Low for age and for post-stroke depression
Response	2; 54	Low RCT Fair	Inconsistent	Indirect	Precise	rTMS > sham in young adult population (ages 18–37) No difference between rTMS and sham for older adults with post-stroke depression Low for age and for post-stroke depression
Remission	1;20	Low RCT Fair	NA	Indirect	Precise	No difference between rTMS and sham in older adults with post-stroke depression Low for post-stroke depression

RCT = randomized controlled trials; rTMS = repetitive transcranial magnetic stimulation

Key Points

We did not identify any head-to-head comparisons for this KQ.

Age

Two studies provide some evidence on the efficacy of nonpharmacologic treatments in two different age groups. One, a Tier 1 study, looked at rTMS in a young adult population (ages 18 to 37); the other was a Tier 3 study in middle-aged subjects (ages 30 to 69) using ECT. A greater decrease in depressive severity and a higher response rate was seen in the trial of severely depressed younger adults undergoing 20 sessions of rTMS compared with sham. However,

efficacy evidence is weaker for the 2-week trial of middle-aged adults with “severe endogenous depression,” where the depressive severity data was only shown in a figure and noted that the completers analysis found a significantly greater decrease in depressive severity with the ECT compared with sham.

Post-stroke Depression

We found one Tier 1 and two Tier 2 trials in older patients with vascular depression. These trials showed a greater decrease in depressive severity in those receiving rTMS treatment versus sham. Two of the three trials found statistically significant improvements, but the third trial was underpowered to detect a difference. Response and remission rates were significantly greater in the active group only for the one trial that provided 15 sessions of rTMS over 3 weeks, in comparison to 10 sessions over 2 weeks in the other trials.

Detailed Analysis

We identified two relevant studies, both involving a comparison to a sham control (Table 87).

Table 87. Efficacy of ECT or rTMS versus sham for age subpopulations: all Tiers, MDD

Author, Year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
Johnstone et al., 1980 ^{68,127,128} 4 weeks, completers Did not require failure in the current episode Tier 3: referred for ECT Fair	ECT (n = 35) Bilateral, 8 sessions Sham (n = 35) Treatment strategy Switch - unclear if patients taking an AD at baseline. No AD allowed during the trial mITT	Previous manic episodes: Overall: 10% Mean number of failed antidepressant trials: ECT: NR Sham: NR Baseline Depression HAM-D ₁₇ , mean (SD) Reported in graph only	HAM-D₁₇ Change, mean (SD) ECT: n= 31 Sham: n = 31 ECT vs. sham $P < 0.01$ (reported in graph only) HAM-D₁₇ Response NR Remission NR	NR
Zheng et al., 2010 ⁷⁵ 4 weeks Did not require failure in the current episode Tier 1 Fair	rTMS (n = 19) High frequency, 20 sessions Sham (n = 15) Treatment strategy Augment – all patients taking escitalopram 2+ weeks before trial	Baseline Depression HAM-D ₁₇ , mean (SD) rTMS: 24.6 (2.9) Sham: 24.6 (2.8) Mean number of failed antidepressant trials: NR	HAM-D₁₇ Change, mean (SD) rTMS: -11.1 Sham: -1.7 $P = \text{NR}$ HAM-D₁₇ Response, n (%) rTMS: 12 (63.2) Sham: 1 (6.7) $P = 0.001$ Remission NR	NR

AD = antidepressants; ECT = electroconvulsive therapy; HAM-D₁₇ = 17 item Hamilton Depression Scale; mITT = modified intent-to-treat analysis; NR = not reported; P = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Age

One Tier 1 trial was conducted in a younger population, ages 18 to 37. An augmentation study, it was a 4-week trial comparing high-frequency rTMS (n = 19) to sham rTMS treatment (n = 15).⁷⁵ At baseline, participants were severely depressed (HAM-D₁₇ mean [SD] rTMS 24.6 [2.9] sham 24.6 [2.8]) and had been taking escitalopram for at least 2 weeks. In an ITT analysis,

participants in the rTMS group had a greater decrease in depressive severity (rTMS -11.1 sham -1.7, $P = \text{NR}$) and a higher response rate (rTMS 63.2% sham 6.7%, $P = 0.001$).

A Tier 3 trial of a middle-aged population (ages 30 to 69) with “severe endogenous depression” referred for ECT compared ECT ($n = 35$) with sham stimulation ($n = 35$) for a period of 4 weeks.⁶⁸ Participants in the study appear to have severe depression but these data are only reported in a graph. It is unclear what proportion of patients were on an antidepressant at study entry or had antidepressant failures in the past. During the trial, patients were not prescribed an antidepressant medication. Based on a completers analysis, the ECT group had a greater decrease in depressive severity compared to the sham group ($P < 0.01$).

Post-stroke Depression

One Tier 1 and two Tier 2 RCTs focus on patients over the age of 50 with MDD and determined to have vascular depression secondary to a vascular accident.^{129,130} As shown in Table 88 below, all three compare high-frequency rTMS to a sham intervention and are of fair quality. All three studies were in moderately to severely depressed study populations (mean HAM-D₁₇ scores between 17 and 20 in each group) and all discontinued any antidepressants they were receiving. No significant differences were reported for headache, local pain, or anxiety. No seizures occurred in either group.

Two experiments are presented in one article where all patients had at least one antidepressant medication failure.¹²⁹ The active intervention in the first study applied 10 sessions of rTMS to 15 patients (15 in the sham group). In a modified ITT analysis after 3 weeks of treatment, the rTMS group had a greater percentage decrease in HAM-D₁₇ (33.1% versus 13.6%, $P = 0.04$) and tended to have a greater response rate, but the difference was not significant. Remission rates in each group were low, but also not significant. The second study increased the number of sessions to 15 and showed a greater decrease in depressive severity in the rTMS group with significantly improved response and remission rates after 3 weeks of treatment. In this experiment, 33 patients received 15 sessions (29 patients in sham group) and resulted in a greater percentage decrease in HAM-D₁₇ (42.4% versus 17.5%, $P = 0.001$), response rate (39.4% versus 6.9%, $P = 0.003$) and remission (27.3% versus 3.4%, $P = 0.01$) in comparison to the sham intervention group.

In the third trial of 20 patients who had two antidepressant trial failures, 10 patients were treated with rTMS over 10 sessions and 10 received the sham treatment.¹³⁰ Those in the rTMS group showed a greater decrease in depressive severity, though the study did not have the power to adequately compare response and remission rates.¹³⁰ Mean baseline depressive severity was moderate, with both groups averaging between 20 and 21 points on the HAM-D₁₇. Antidepressants were tapered to discontinuation prior to enrollment, so patients were switched to rTMS or control. An ITT analysis at 3 weeks found that outcomes favored the rTMS group. Compared to control, rTMS produced a greater decrease in depressive severity (-7.3 versus -2.7, $P < 0.006$) and a greater likelihood of both response (3 out of 10 versus 0 out of 10) and remission (1 of 10 versus 0 of 10).

Table 88. Efficacy and other comparative harms outcomes of rTMS versus sham in post-stroke depression subpopulations: all Tiers, MDD

Author, year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
<p>Jorge et al., 2008¹²⁹ Experiment 1 RCT, primary endpoint at 3 weeks, mITT Failure required in current episode Tier 2 Fair</p>	<p>rTMS (n = 15) High frequency, 10 sessions Sham (n = 15) Concurrent medications All antidepressants discontinued Strategy Switch Definitions Remission: HAM-D₁₇ < 8 and did not meet criteria for major or minor depression</p>	<p>Subgroup Patients with stroke/cerebral vascular disease Diagnosis, % MDD: 100 Baseline Depression: HAM-D₁₇ rTMS: 19.5 (5.8) Sham: 19.9 (5.4)</p>	<p>HAM-D₁₇ Response, n (%) rTMS: 5 (33.3) Sham: 1 (6.7) <i>P</i> = 0.08 Remission, n (%) rTMS: 2 (13.3) Sham: 1 (6.7) <i>P</i> = 0.5 Change, % rTMS: -33.1 Sham: -13.6 <i>P</i> = 0.04</p>	<p>Adverse Events Headache, % rTMS: 5 (33) Sham: 4 (27) <i>P</i> = NR No differences in frequency of headaches; all headaches were mild and responded to low dose analgesics Local Pain, n (%) rTMS: 1 (7) Sham: 1 (7) <i>P</i> = NR Local discomfort, n (%) rTMS: 4 (27) Sham: 5 (33) No difference in frequency of local discomfort <i>P</i> = NR Anxiety, n (%) rTMS: 2 (13) Sham: 0 (0) <i>P</i> = NR Seizures, n rTMS: 0 Sham: 0 <i>P</i> = NR</p>
<p>Jorge et al., 2008¹²⁹ Experiment 2 RCT, primary endpoint at 3 weeks, mITT Failure required in current episode Tier 2 Fair</p>	<p>rTMS (n = 33) High frequency, 15 sessions Sham (n = 29) Concurrent medications All antidepressants discontinued Strategy Switch Definitions Remission: HAM-D₁₇ < 8 and did not meet criteria for major or minor depression</p>	<p>Subgroup Patients with stroke/cerebral vascular disease Diagnosis, % MDD: 100 Baseline Depression, n (%): HAM-D₁₇ rTMS: 18.4 (3.4) Sham: 17.6 (5.6)</p>	<p>HAM-D₁₇ Response, n (%) rTMS: 13 (39.4) Sham: 2 (6.9) <i>P</i> = 0.003 Remission rTMS: 9 (27.3) Sham: 1 (3.4) <i>P</i> = 0.01 Change, % rTMS: -42.4 Sham: -17.5 <i>P</i> < 0.001</p>	<p>Adverse Events Headache, % rTMS: 7 (21) Sham: 3 (10) No differences between groups in frequency of headaches; all headaches were mild and responded to low dose analgesics <i>P</i> = NR Local Pain, n (%) rTMS: 1 (3) Sham: 0 (0) <i>P</i> = NR Local discomfort, n (%) rTMS: 3 (9) Sham: 1 (3) No difference in frequency of local discomfort <i>P</i> = NR Anxiety, n (%) rTMS: 0 (0) Sham: 0 (0) <i>P</i> = NR Seizures, n rTMS: 0 Sham: 0 <i>P</i> = NR</p>

Table 88. Efficacy and other comparative harms outcomes of rTMS versus sham in post-stroke depression subpopulations: all Tiers, MDD (continued)

Author, year Study Design Primary Endpoint(s) Quality	Intervention and Sample Size Study Details	Population Characteristics	Response Remission Change in Depressive Symptoms	Adverse Events Quality of Life Attrition
Jorge et al., 2004 ¹³⁰ RCT, primary outcome at 3 weeks (2 weeks of txt, 1 week followup), ITT Failure in current episode not required Tier 1 Fair	rTMS (n = 10) High frequency, 10 sessions Sham (n = 10) Concurrent Medications All antidepressant medications discontinued Strategy Switch	Subgroup Patients with stroke/cerebral vascular disease Diagnosis,% MDD: 85 Minor depression: 15 Baseline Depression: HAM-D ₁₇ rTMS: 20.1 (6.7) Sham: 20.8 (6.0)	HAM-D₁₇ Response, n (%) rTMS: 3 (30) Sham: 0 (0) <i>P</i> = NS Remission, n (%) rTMS: 1 (10) Sham: 0 (0) <i>P</i> = NS Change Score rTMS: 7.3 Sham: NR (can be calculated as 2.7) <i>P</i> < 0.006 Change,% rTMS: -38 Sham: -13	Adverse Events No significant differences in frequency of adverse events between active and sham rTMS groups Neither group reported seizures or propagation of cortical excitability to ipsilateral motor cortex

HAM-D₁₇ = 17-item Hamilton Depression Scale; ITT = intent-to-treat analysis; MDD = major depressive disorder; mITT = modified intent-to-treat analysis; NR = not reported; NS = not significant; *P* = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; txt = treatment

Key Question 6: Health-Related Outcomes—Overview

Understanding the burden of affective disorders on the quality of life of patients is an important component to establishing the overall effectiveness of treatment for these disorders. However, quality of life is rarely assessed in this body of literature. Previous ECT studies have associated ECT with a post-treatment quality-of-life improvement that can be maintained from 1 month to 1 year.⁶¹ Very little quality-of-life data following rTMS, VNS, behavioral, or other nonpharmacologic treatments are available.

Numerous psychometric measures exist to assess an individual's level of functioning and execution of daily living activities, which are both health domains that are related to quality of life. The Global Assessment of Functioning (GAF) and the Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) are scales used to determine patients' ability to function in daily life.^{131,132} The Medical Outcomes Study 36 Item Short Form (MOS SF-36 or SF-36) is an internationally recognized generic health survey instrument comprised of 36 items in eight independent health domains used to survey the health status of an individual.¹³³ The Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q) is a 16-item questionnaire that uses a self-report measure to obtain the degree of enjoyment and satisfaction of various areas of daily functioning.^{134,135} Finally, the Social Adjustment Scale-Self-Report (SAS-SR) work subscale taps a subset of daily activities that may indirectly reflect patients' quality of life.¹³⁶

The following KQ focuses on the comparative benefit of patient-reported health-related outcomes using quality of life measures with TRD (MDD/bipolar and MDD-only). There were no head-to-head (direct) comparisons identified. Four indirect comparison studies were available and assessed general health status and mental and physical functioning. Two studies compared

rTMS versus sham, one study compared VNS versus sham, and one study compared CBT versus control.

For TRD populations (Tier 1), we identified two studies, both in MDD/bipolar mix samples (Table 89), one comparing rTMS versus sham⁸⁰ and one comparing VNS versus sham.⁹⁸ Both studies suggested greater benefit for rTMS over the control. An additional study compared MDD patients comparing ECT versus ECT plus rTMS.⁶⁴

Table 89. Number of good- and fair-quality studies by TRD tier and diagnostic mix for KQ 6

Comparison	Tier	MDD-only	MDD and Bipolar Disorder
ECT vs. rTMS	Tier 2: ≥ 1 treatment failure	1	0
rTMS vs. Sham	Tier 1: ≥ 2 treatment failures	0	1
rTMS vs. Sham	Tier 2: ≥ 1 treatment failure	0	1
VNS vs. Sham	Tier 1: ≥ 2 treatment failures	0	1
CBT vs. Control	Tier 2: ≥ 1 treatment failure	2	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic simulation; VNS = vagus nerve stimulation; vs. = versus

Considering additional tiers added two Tier 2 studies of MDD-only populations comparing CBT versus control group^{93,94} that showed no difference in outcomes (Table 89). Additionally, a study that compared rTMS to sham is in Tier 2 and suggests an increase in quality of life in the active group using the SF-36 and the Q-LES-Q.^{87,115,116,119,124,125} A tier 2 study conducted in 40 patients comparing ECT to rTMS illustrated improvements in quality of life using the GAF.¹¹⁸

Strength of Evidence: Tier 1 (TRD)

One study directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes. The study shows no difference in quality of life that compared ECT to ECT plus rTMS.⁶⁴ No evidence directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes. Three studies provided indirect evidence. Neither of these two Tier 1 studies assessed quality of life for a nonpharmacologic intervention versus control, instead assessing general health status and mental and physical functioning, and related health domains, for a nonpharmacologic treatment versus sham comparison. One study provided insufficient strength of evidence to assess whether there was a greater improvement in the ability to function following treatment with rTMS compared to sham, as results were mixed (Table 90).⁸⁰ Results were in the same direction favoring rTMS, but one of the active arms (low-right rTMS) produced statistically greater improvement than sham, while the second active arm (high-left rTMS) produced greater improvement that did not reach statistical significance. The other study provided low strength of evidence that health status did not differ significantly following treatment with VNS or sham.⁹⁸

Table 90. Strength of Evidence: Health-related outcome measures – Tier 1

Comparison	Number of studies; subjects	Risk of bias Design Quality	Consistency	Directness	Precision	Results and Strength of Evidence
ECT vs. ECT + rTMS	1, 22	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	No difference between groups in improvements to daily functioning Low
rTMS vs. sham	1; 60	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	High-left rTMS produces greater improvement in health status and daily functioning than sham ($P = 0.09$) Low rTMS produces greater improvement in health status and daily functioning than sham ($P = 0.03$) Low
VNS vs. sham	1; 214	Medium 1 RCT 1 Fair	Unknown	Indirect	Imprecise	No difference between VNS vs. sham in daily functioning Low

ECT = electroconvulsive therapy; NA = not applicable; P = p-value; RCT = randomized controlled trial; rTMS = transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Key Question 6: Health-Related Outcomes-Key Points

One study directly compared the effect of nonpharmacologic treatment on patient-reported health-related outcomes (ECT to ECT plus rTMS study).⁶⁴

We identified five relevant studies that compared outcomes related to quality of life for patients who underwent rTMS or VNS versus sham, or CBT compared to a control group. Three studies^{87,93,94,115,116,119,124,125} involved patients with MDD-only, and the other two studies^{80,98} involved patients with MDD and/or bipolar disorder. The studies were funded by the United States federal government, hospitals, and universities. The active treatment duration across studies ranged from 2 to 16 weeks.

Overall, the study samples were relatively small; two of the four studies had study samples of 50 or fewer patients, but one had a study sample of 491. All studies were RCTs and were rated as fair quality. One study found statistically significant differences in GAF between one active arm and sham, but not between the other active arm and sham.⁸⁰ Additionally, two studies reported significant changes ($P < 0.05$) in the SAS-SR work subscale and the SF-36 Mental Component Score and the Q-LES-Q Total Score, respectively.^{87,93,115,116,119,124,125}

Key Question 6: Health-Related Outcomes—Detailed Analysis

Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Tier 1

No Tier 1 data were available for either the MDD-only or MDD/bipolar populations.

Tier 2. Patients With one or More Treatment Failures

MDD-Only

One study compared ECT versus rTMS in 40 patients (Table 91).⁵⁹ The study used the GAF to measure changes in functioning in the patients. Though both groups showed improvement from baseline, there were no between group differences in the measure.

Table 91. Quality of life of ECT versus rTMS: Tier 2, MDD

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Grunhaus et al., 2003 ⁵⁹ RCT Did not specify failure in the current episode 4 weeks Fair	ECT (n = 20) 35% bilateral, mean sessions 10.25 (SD 3.1) rTMS (n = 20) High frequency, 20 sessions (4 weeks)	Global Assessment of Functioning (GAF) Baseline score, mean (SD) ECT: 39.8 (9.3) rTMS: 48.9 (10.8) Endpoint score, mean (SD) ECT: 60.6 (13.5) rTMS: 62.5 (18.8) Group by time interaction, P = NS

ECT = electroconvulsive therapy; NS = not significant; P = p-value; RCT = randomized controlled trial; rTMS = transcranial magnetic stimulation; SD = standard error

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Electroconvulsive Therapy Versus Electroconvulsive Therapy Plus Repetitive Transcranial Magnetic Stimulation

Tier 1. Patients With two or More Treatment Failures

MDD-Only

One study compared ECT and an ECT plus rTMS using the GAF to assess quality of life (Table 92).⁶⁴ The intervention groups did not differ significantly on the final score.

MDD/Bipolar

No data available.

Tier 2

No Tier 2 data were available for either the MDD-only or MDD/bipolar populations.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 92. Quality of life of ECT versus ECT plus rTMS: Tier 1, MDD

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Pridmore et al., 2000 ⁶⁴ RCT 2 to 4 weeks Did not specify failure in the current episode Fair	ECT (n = 11) 100% unilateral, 6 sessions ECT plus rTMS (n = 11) ECT: 100% unilateral (day 1), plus high-frequency rTMS: (days 2-5) Repeated in week 2; 8 sessions	Global Assessment of Functioning Baseline score, median ECT: 41 ECT plus rTMS: 41 Endpoint (at 2 weeks) score, median (SD) ECT: 70 ECT plus rTMS: 65 Comparison of median difference between groups, <i>P</i> = NS

ECT = electroconvulsive therapy; NS = not significant; P = p-value; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Repetitive Transcranial Magnetic Stimulation Versus Sham

Tier 1: Patients With two or More Treatment Failures

MDD-Only

There were no eligible studies.

MDD/Bipolar

One study compared rTMS treatment (two versions—LFR-rTMS and HFL-rTMS) to a sham procedure and found no significant differences between the active rTMS groups compared with the sham group in the GAF mean score change (Table 93).⁸⁰ However, they found a statistically significant difference in the GAF mean score change between the LFR-rTMS versus sham groups (*P* = 0.03), though the difference is not clinically significant as all groups remained in the 41–50 point range, which is rated as serious symptoms (e.g., suicidal ideation, severe obsessional rituals, frequent shoplifting) or any serious impairment in social, occupational, or school functioning (e.g., no friends, unable to keep a job).¹³⁷

Tier 2: Patients With one or More Treatment Failures

MDD-Only

One study compared rTMS to sham procedure and found significant differences between the two groups in both the SF-36 mental component score (*P* = 0.032) and the Q-LES-Q total score (*P* = 0.035) (Table 94).^{87,115,116,119,125,138} These changes are small and their clinical significance is unclear.

MDD/Bipolar

There were no eligible studies.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Vagus Nerve Stimulation Versus Sham

Tier 1. Patients With two or More Treatment Failures

MDD-Only

There were no eligible studies.

MDD/Bipolar

One study compared VNS and a sham procedure using the MOS SF-36 to assess quality of life (Table 95).⁹⁸ The intervention and control groups did not differ significantly on either the mental or physical components of the MOS SF-36 instrument.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 93. Quality of life of rTMS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Fitzgerald et al., 2003 ⁸⁰ 2 weeks, all reported patients included Did not require failure in the current episode Fair	High-rTMS (n = 20) High frequency, 10 sessions Low-rTMS (n = 20) Low frequency, 10 sessions Sham (n = 20)	Global Assessment of Functioning Baseline score, mean (SD) High rTMS: 43.0 (6.8) Low rTMS: 43.5 (9.9) Sham: 42.7 (7.1) Endpoint score, mean (SD) At week 2 High rTMS: 45.2 (7.1) Low rTMS: 46.3 (8.5) Sham: 42.5 (6.8) Change, mean At week 2 High rTMS: 2.2 Low rTMS: 1.4 Sham: 0.2 High rTMS vs. sham: $P = 0.09$ Low rTMS vs. sham: $P = 0.03$

n = number; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation; VNS = vagus nerve stimulation; vs = versus

Table 94. Quality of life of rTMS versus sham: Tier 2, MDD and ≤ 20 percent bipolar disorder

Author, Year Study Design Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
<p>O'Reardon et al., 2007,⁸⁷ Janicak et al., 2007,¹¹⁵ and Solvason et al., 2007¹¹⁶ RCT 6 weeks, all reported patients included Required to have failed at least one in this or most recent episode or four failed attempts in lifetime. Fair</p>	<p>rTMS (n=155) High frequency, up to 30 sessions Sham (n=146)</p>	<p>Medical Outcomes Study Short Form-36 Mental Component Score, mean (SD) Baseline score rTMS: 20.4 (8.05) Sham: 20.4 (7.76) Change at week 6 rTMS: 5.7 (12.65) Sham: 2.9 (10.6) <i>P</i> = 0.032 Physical Component Score, mean (SD) Baseline score rTMS: 50.5 (11.01) Sham: 48.8 (10.35) Change at week 6 rTMS: 0.1 (7.49) Sham: -0.2 (7.23) <i>P</i> = 0.682 Quality of Life, Enjoyment and Satisfaction Questionnaire –Short Form Baseline score, mean (SD) rTMS: 37.8 (8.23) Sham: 36.5 (7.87) Endpoint score, mean (SD) At week 6 rTMS: 42.2 (12.28) Sham: 39.0 (10.15) Change, mean At week 6 rTMS: 2.0 (9.24) Sham: 1.3 (9.85) <i>P</i> = 0.035</p>

n = number; P = p-value; RCT = randomized controlled trial; rTMS = repetitive transcranial magnetic stimulation; SD = standard deviation

Table 95. Quality of life of VNS versus sham: Tier 1, MDD and ≤ 20 percent bipolar disorder

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
<p>Rush et al., 2005⁹⁸ 10 weeks Two to six failures in current episode. Fair</p>	<p>VNS (n = 112) 10 weeks of VNS therapy with continued medications Sham (n = 110) Sham: device implanted but not turned on</p>	<p>Medical Outcomes Study Short Form-36 Analyzed, n VNS: 107 Sham: 107 Physical component, change mean (SD) VNS: -0.9 (8.3) Sham: -1.6 (8.4) <i>P</i> = 0.480 Mental component, change mean (SD) VNS: 5.0 (11.6) Sham: 4.0 (10.2) <i>P</i> = 0.406</p>

n = number; P = p-value; SD = standard deviation; VNS = vagus nerve stimulation

Cognitive Behavioral Therapy Versus Control

Tier 1

No Tier 1 data were available for either the MDD-only or MDD/bipolar populations.

Tier 2. Patients With one or More Treatment Failures

MDD-Only

The Harley et al. study, rated fair quality, compared patients receiving psychotherapy such as CBT or IPT with a control group using the LIFE-RIFT instrument (Table 96).⁹³ They found no significant differences between the intervention and control groups. They also used the SAS-SR work subscale as a measure of quality of life, reporting a significant difference ($P < 0.05$) between the psychotherapy group compared with the control group.

A larger study in 491 participants compared three interventions, two forms of psychotherapy used in conjunction with medication and just medication with no psychotherapy.⁹⁴ It measured quality of life using LIFE-RIFT and found no differences between the interventions.

MDD/Bipolar

There were no eligible studies.

Tier 3

No Tier 3 data were available for either the MDD-only or MDD/bipolar populations.

Table 96. Quality of life of CBT versus control: Tier 2, MDD

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Harley et al., 2008 ⁹³ 16 weeks, all reported patients included Did not require failure in the current episode Fair	CBT [DBT] (n = 10) 16 weekly sessions of dialectical behavior therapy skills training Control (n = 9) Waitlist	Lifework-The Range of Impaired Functioning Tool Change, mean (SD) CBT: -1.3 Control: -0.33 $P = NS$ Social Adjustment Scale-Self-Report (SAS-Self Report) work subscale Baseline score, mean (SD) CBT/DBT: 82.50 (21.21) Control: 69.22 (17.95) Endpoint score, mean (SD) CBT/DBT: 65.70 (19.27) Control: 69.56 (17.66) Change, mean CBT/DBT: -16.80 Control: 0.34 $P < 0.05$

Table 96. Quality of life of CBT versus control: Tier 2, MDD (continued)

Author, Year Endpoint Episode Failure Quality	Intervention and Sample Size Study Details	Results
Kocsis et al., 2009 ⁹⁴ RCT 12 weeks Fair	CBASP (n=200) Cognitive behavioral analysis system of psychotherapy plus medication; 16-20 sessions BSP (n=195) Brief Supportive Psychotherapy; usual medication; 16-20 sessions No psychoterapy (n=96) Medication only	Life-Rift Sore Baseline score, mean (SD) CBASP: 12.69 (2.96) BSP: 12.71 (3.14) No psychotherapy: 12.64 (3.01) Endpoint score, mean (SD) CBASP: 10.24 (3.25) BSP: 10.73 (3.46) No psychotherapy: 10.96 (3.63) Difference, mean CBASP: 2.45 BSP: 1.98 No psychotherapy: 1.68 No difference between comparisons

BSP = brief supportive psychotherapy; CBASP = cognitive behavioral analysis system of psychotherapy; CBT = cognitive behavioral therapy; DBT = dialectical behavior therapy; Lifework-RIFT = Lifework-The Range of Impaired Functioning Tool; SD = standard deviation

Discussion

Background

This review from the RTI International–University of North Carolina at Chapel Hill Evidence-based Practice Center provides a comprehensive summary of the available data addressing the comparative effectiveness of four nonpharmacologic treatments—electroconvulsive therapy (ECT), repetitive transcranial magnetic stimulation (rTMS), vagus nerve stimulation (VNS), and cognitive behavioral therapy (CBT) or interpersonal psychotherapy—as therapies for patients with treatment-resistant depression (TRD). For one issue (see key questions [KQs] below), we also examined pharmacologic (antidepressant) interventions. The core patient population of interest was patients with major depressive disorder (MDD) who met our definition of TRD: failure to respond following two or more adequate antidepressant trials. We also included studies in which the patient population could include a “mix” of up to 20 percent of patients with bipolar disorder (i.e., 80 percent or more of patients had only MDD), assuming that this small mix would not substantially alter outcomes seen with MDD-only populations. In addition, we distinguished between patients for whom treatment was directed at the acute phase of disease and those for whom treatment was intended to maintain remission or to prevent relapse.

We structured our review to focus chiefly on our primary population of interest (MDD patients with TRD) but also considered data from studies that likely had a substantial proportion of TRD patients. We worked with our Technical Expert Panel to identify different tiers of definitions for TRD to use in our analytic strategy:

- **Tier 1** evidence (TRD as defined in this report): studies in which patients specifically had two or more prior treatment failures with medications.
- **Tier 2** evidence: studies in which patients had one or more prior treatment failures.
- **Tier 3** evidence: studies in which the number of prior treatment failures was not specified but the clinical situation suggested a high probability of patients having two or more prior antidepressant treatment failures; this data has probable relevance to TRD. Studies which did not specify the number of failed treatments but noted that all subjects were referred for ECT were included in this tier.

The focus of each of the six KQs or subquestions is listed below (key distinguished elements in italics).

- KQ 1a. Efficacy of nonpharmacologic interventions for *acute-phase* TRD (depressive severity, response, or remission).
- KQ 1b. Efficacy of nonpharmacologic versus pharmacologic interventions for *acute-phase* TRD (depressive severity, response, or remission), for patients with two or more prior treatment failures.
- KQ 2. Efficacy of nonpharmacologic interventions for *maintaining response or remission* with respect to TRD (e.g., preventing relapse or recurrence).
- KQ 3. Efficacy of nonpharmacologic interventions for *acute-phase* TRD as a function of particular *symptom subtypes* (e.g., catatonia or psychosis).
- KQ 4. Harms of nonpharmacologic interventions (i.e., safety, adverse events, or adherence issues).
- KQ 5. Efficacy or harms of nonpharmacologic treatments for selected patient subgroups defined by sociodemographic characteristics or coexisting conditions.

- KQ 6. Health-related outcomes of nonpharmacologic treatments (e.g., quality of life).

In the discussion below, we comment on findings from direct and indirect evidence for clearly defined TRD (Tier 1); where differences were clinically meaningful, we provide the data also reported in Results. Respectively, these terms refer to head-to-head studies or studies involving a control group of some sort, such as a sham procedure or usual care (treatment as usual). As with Results, we include only studies for which we rated the quality as either good or fair; most studies were of only fair quality.

Finally, we graded the strength of evidence for major outcomes and comparisons for the clearly defined TRD population (Tier 1). Detailed information for data from all three tiers was presented in Results, and the reader can refer to the detailed analysis sections in Results for evidence involving Tier 2 and Tier 3 studies. Below, we comment in text about the strength of evidence for the main findings specifically for TRD. To recap, the four levels of strength of evidence are as follows:

1. **High: High confidence that the evidence reflects the true effect.** Further research is very unlikely to change our confidence in the estimate of effect.
2. **Moderate: Moderate confidence that the evidence reflects the true effect.** Further research may change our confidence in the estimate of effect and may change the estimate.
3. **Low: Low confidence that the evidence reflects the true effect.** Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
4. **Insufficient:** Evidence either is unavailable or does not permit estimation of an effect.

Overview of Main Findings

Summaries of our main findings are found in Table 97 through Table 106. If a specific comparison did not involve a Tier 1 population but did have trials conducted in a Tier 2 and/or Tier 3 population, we have listed it in this table, noted “No eligible studies identified,” and added a footnote indicating the presence of at least one such study.

Table 97. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a. comparative efficacy of nonpharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. rTMS	Change in depressive severity	42	Low	1 fair trial: both ECT and rTMS improved symptom severity but did not differ significantly.
ECT vs. rTMS	Response rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT vs. rTMS	Remission rate	42	Low	1 fair trial: ECT and rTMS did not differ significantly.
ECT plus rTMS vs. ECT	Change in depressive severity	22	Low	1 fair trial: both ECT and ECT plus rTMS improved symptom severity but did not differ significantly.
ECT plus rTMS vs. ECT	Response rate	0	NA	No eligible studies identified. ‡
ECT plus rTMS vs. ECT	Remission rate	22	Low	1 fair trial: ECT and ECT plus rTMS did not differ significantly.
ECT vs. sham	Change in depressive severity	0	NA	No eligible studies identified. ‡
ECT vs. sham	Response rate	0	NA	No eligible studies identified. ‡

Table 97. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for Key Question 1a. comparative efficacy of nonpharmacologic treatments (continued)

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. sham	Remission rate	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Change in depressive severity	497	High	7 trials (3 good, 4 fair): rTMS had a significantly greater decrease in depressive severity than sham. 4 fair trials: rTMS had nonsignificantly greater decrease in depressive severity than sham. 2 fair trials: rTMS had greater decrease than sham but significance NR. 1 fair trial: rTMS did not significantly differ from sham.
rTMS vs. sham	Response rate	471	High	4 trials (3 good, 1 fair): rTMS had a significantly higher response rate than sham. 1 fair trial: rTMS had a nonsignificantly higher response rate than sham. 6 fair trials: rTMS had a higher response rate than sham, but significance NR. 1 fair trial: rTMS did not clearly differ from sham, but significance NR.
rTMS vs. sham	Remission rate	223	Moderate	3 trials (2 good, 1 fair): rTMS had significantly greater remission rate than sham. 2 fair trials: rTMS had a greater remission rate than sham but significance NR.
VNS vs. sham	Change in depressive severity	235	Low	1 good trial: VNS and sham did not differ significantly.
VNS vs. sham	Response rate	235	Low	1 good trial: VNS and sham did not differ significantly.
Psychotherapy vs. control	Change in depressive severity	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. control	Response rate	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. control	Remission rate	0	NA	No eligible studies identified. [‡]

ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on the EPC program's modified version of the GRADE system; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 or Tier 3 study addressed this comparison.

Table 98. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 1b. comparative efficacy of nonpharmacologic and pharmacologic treatments

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. pharmacotherapy	Change in depressive severity	39	Low	1 fair trial: ECT had significantly greater improvement in symptom severity than pharmacotherapy.
ECT vs. pharmacotherapy	Response rate	39	Low	1 fair trial: ECT had significantly greater response rates than pharmacotherapy.
Psychotherapy vs. pharmacotherapy	Change in depressive severity	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. pharmacotherapy	Response rate	0	NA	No eligible studies identified. [‡]
Psychotherapy vs. pharmacotherapy	Remission rate	0	NA	No eligible studies identified. [‡]

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 99. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 2. comparative efficacy for maintaining remission

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
ECT vs. rTMS	Maintenance of remission	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Maintenance of remission	68	Insufficient	3 fair trials: no significant differences in maintenance of remission however, small sample sizes in two of the studies and the presence of a co-intervention in the third study make results difficult to interpret
CBT vs. usual care	Maintenance of remission	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews system; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 100. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 3. comparative efficacy for particular symptom subtypes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings [†]
ECT vs. rTMS	Change in depressive severity	0	NA	No eligible studies identified. [‡]

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 101. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4a. impact of nonpharmacologic interventions on cognitive functioning

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Cognitive functioning	72	Insufficient	1 fair trial and 1 fair cohort study: Some evidence suggests no difference between treatments, whereas some evidence suggests ECT may have deleterious impact on cognitive functioning compared with rTMS (1 study: significant effect on 1-week recall; both studies: nonsignificant effect on all other measures).
ECT vs. ECT + rTMS	Cognitive functioning	22	Insufficient	1 fair trial: no significant differences in a single item measure on memory problems
rTMS vs. sham	Cognitive functioning	101	Insufficient	3 trials (1 good, 2 fair): Some evidence suggests no difference between rTMS and sham, whereas some evidence suggests that rTMS improves cognitive functioning compared to sham (2 trials: significant differences in memory, verbal fluency; all other findings nonsignificant or significance not reported)

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

Table 102. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4b. specific adverse events

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Adverse events	0	NA	No eligible studies identified. [‡]
ECT vs. ECT + rTMS	Adverse events	22	Low	1 fair trial: no significant differences in specific adverse events
rTMS vs. sham	Adverse events	68	Low	1 good trial: rTMS resulted in significantly more scalp pain at the stimulation site than sham.
VNS vs. sham	Adverse events	235	Low	1 fair trial: Some differences in specific adverse events reported ($P = NR$)

ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 103. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4c. withdrawals due to adverse event

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Withdrawals	30	Low	1 fair cohort study: no difference in withdrawals between ECT and rTMS groups ($P = NR$).
ECT vs. sham	Withdrawals	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Withdrawals	277	Insufficient	7 trials (1 good, 6 fair): trials showed mixed results about withdrawals attributed to adverse events.
VNS vs. sham	Withdrawals	235	Low	1 good trial: VNS had greater withdrawals attributed to adverse events than sham (significance NR).
CBT vs. usual care	Withdrawals	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; NR = not reported; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 104. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 4d. adherence as measured by overall withdrawals

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
ECT vs. rTMS	Overall withdrawals	72	Low	1 fair trial and 1 fair cohort study: studies showed more withdrawals in ECT group compared with sham ($P = NR$).
ECT vs. sham	Overall withdrawals	0	NA	No eligible studies identified. [‡]
rTMS vs. sham	Overall withdrawals	325	Insufficient	8 fair trials: trials showed mixed results about withdrawals.
CBT vs. usual care	Overall withdrawals	0	NA	No eligible studies identified. [‡]

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

[‡]At least one Tier 2 and/or Tier 3 study addressed this comparison.

Table 105. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 5. efficacy and harms for selected populations

Comparison	Outcome	Number of Subjects	Strength of Evidence	Findings [†]
rTMS vs. sham	Changes in depressive severity	34	Low	1 fair trial: rTMS produced better outcome than sham in young adult population (ages 18–37).
rTMS vs. sham	Changes in depressive severity	20	Low	1 fair trial: rTMS produced better outcome than sham in older adults with post-stroke depression.
rTMS vs. sham	Response	34	Low	1 fair trial: rTMS produces better response rates than sham in young adult population (ages 18–37).
rTMS vs. sham	Response	20	Low	1 fair trial: no difference between rTMS and sham for older adults with post-stroke depression.
rTMS vs. sham	Remission	20	Low	1 fair trial: no difference between rTMS and sham in older adults with post-stroke depression.

rTMS = repetitive transcranial magnetic stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

[†]Good and fair designations relate to quality ratings for each study.

Table 106. Summary of findings on nonpharmacologic treatment of adult treatment-resistant depression (TRD) with strength of evidence for Tier 1 (TRD) for KQ 6. health-related outcomes

Comparison	Outcome	Number of Subjects	Strength of Evidence*	Findings†
ECT vs. ECT + rTMS	Health-related outcomes	22	Low	There were no differences between groups in improvements in daily functioning.
rTMS vs. sham	Health-related outcomes	60	Low	1 fair trial: low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham.
VNS vs. sham	Health-related outcomes	214	Low	1 fair trial: VNS and sham groups did not differ significantly in daily functioning.
CBT/DBT vs. control	Health-related outcomes	0	NA	No eligible studies identified. ‡

CBT = cognitive behavioral therapy; DBT = dialectical behavioral therapy; NA = not applicable; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

*Strength of evidence is based on guidance provided in the AHRQ Methods Guide for Comparative Effectiveness Reviews; see text.

†Good and fair designations relate to quality ratings for each study.

‡At least one Tier 2 and/or Tier 3 study addressed this comparison.

KQ 1a: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Each Other in TRD Populations (Tier 1)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions for Tier 1 TRD is limited to two fair trials (both in MDD-only populations) (Table 107). One compared ECT and rTMS, and the other compared ECT and ECT plus rTMS. They showed, with low strength of evidence, no differences between treatment options for depressive severity, response rates, and remission rates. No trial involved a direct comparison of VNS or psychotherapy with another nonpharmacologic intervention.

Table 107. Number of Tier 1 (TRD) studies of head-to-head comparisons of nonpharmacologic treatments, by comparison

Comparison	Number
ECT plus rTMS vs. ECT	1
ECT vs. rTMS	1

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation

Indirect Evidence

We identified trials that compared a nonpharmacologic intervention, generally rTMS, VNS, or psychotherapy, with a control or sham procedure in Tier 1 populations. We identified no eligible ECT versus control studies (Table 108). The number of these trials with the same or similar control group was very small, so we could not pool them quantitatively. We could, however,

assess the potential benefits of nonpharmacologic interventions versus controls by calculating mean changes in depressive severity, relative risks of response, and relative risks of remission.

rTMS was beneficial relative to controls receiving a sham procedure for all three outcomes (severity of depressive symptoms, response rate, remission rate). rTMS produced a greater decrease in depressive severity (high strength of evidence). Specifically, rTMS averaged a decrease in depressive severity measured by the Hamilton Rating Scale for Depression (HAM-D) of more than 5 points relative to sham control, and this change meets the minimum threshold of the 3-point HAM-D difference that is considered clinically meaningful. Response rates were greater with rTMS than sham (also high strength of evidence); those receiving rTMS were more than 3 times as likely to achieve a depressive response as patients receiving a sham procedure. Finally, rTMS was also more likely to produce remission than the control procedure (moderate strength of evidence); patients receiving rTMS were more than 6 times as likely to achieve remission as those receiving the sham.

In the only other Tier 1 comparison, one good-quality VNS versus sham control trial (a mixed MDD/bipolar population) reported no differences between the groups as measured by a change in depressive severity or response rates (low strength of evidence).

KQ 1b: Efficacy of Acute-Phase Interventions: Nonpharmacologic Interventions Against Medications in TRD Populations (Tier 1)

Direct Evidence

The available head-to-head literature concerning the efficacy of the nonpharmacologic interventions compared with pharmacologic treatment (in this case, paroxetine) for Tier 1 trials is limited to one fair trial (a mixed MDD/bipolar population). ECT produced a significantly greater decrease in depressive severity (9 points by HAM-D) and significantly better response rates (71% vs. 28%) than medications (low strength of evidence) (Table 109).

Table 108. Number of Tier 1 (TRD) studies of nonpharmacologic interventions against controls or usual care, by comparison

Intervention and Control	Number
ECT vs. sham	0
rTMS vs. sham procedure	15
VNS plus usual care vs. usual care	1
Psychotherapy plus usual care vs. usual care	0

ECT = electroconvulsive therapy; rTMS = repetitive transcranial magnetic stimulation; VNS = vagus nerve stimulation; vs. = versus

Table 109. Number of Tier 1 (TRD) studies involving pharmacotherapy, by comparison

Intervention	Number
ECT vs. pharmacotherapy	1
CBT vs. pharmacotherapy	0

CBT = cognitive behavioral therapy; ECT = electroconvulsive therapy; vs. = versus

Indirect Evidence

Indirect evidence about procedures or psychotherapy (vs. sham or nonpharmacological controls) were presented above as part of KQ 1.

We attempted to determine mean changes in depressive severity, relative risks of response, and relative risks of remission for pharmacologic versus control studies to allow a comparison with similar outcomes in the nonpharmacologic versus control trials (KQ 1a, indirect). However, there were no comparable, common control groups not receiving a mood-related medication to allow such comparisons.

Instead, we determined mean average outcomes for pharmacologic treatments.

- For switching strategies, mean pharmacologic response rates averaged 39.8 percent (95% CI, 30.7–48.9) and mean remission rates averaged 22.3 percent (95% CI, 16.2–28.4);
- For augmentation, mean response rates averaged 38.1 percent (95% CI, 31.0–45.3) and mean remission rates average 27.2 percent (95% CI, 20.4–34.0); and
- For maintenance strategies, mean response rates averaged 27.3 percent (95% CI, 19.8–34.8) and mean remission rates averaged 16.8 percent (95% CI, 13.5–20.2).

Although these results provide an idea of the general degree of response seen with next-step pharmacologic treatment in TRD, they serve as an uncontrolled case series and should only be compared to nonpharmacologic outcomes with caution.

KQ 2. Efficacy of Nonpharmacologic Interventions for Maintenance of Remission or Prevention of Relapse in TRD Populations (Tier 1)

Direct Evidence

With respect to maintaining remission (or preventing relapse), there were no direct comparisons involving ECT, rTMS, VNS, or CBT.

Indirect Evidence

Three fair trials compared rTMS with a sham procedure and found no significant differences, however, too few patients were followed during the relapse prevention phases in two of the three studies and patients in the third received a co-intervention providing insufficient evidence for a conclusion. We had no eligible studies for ECT, VNS, or psychotherapy.

KQ 3. Efficacy of Nonpharmacologic Interventions for Patients with Different Symptomatology in TRD Populations (Tier 1)

Direct Evidence

We identified no Tier 1 trials that addressed whether procedure-based treatments differed as a function of symptom subtypes. Also, no comparative evidence was available about psychotherapy in subgroups defined by symptom clusters.

Indirect Evidence

We identified no studies testing either procedure-based or psychotherapeutic interventions against sham procedures or other controls.

KQ 4. Harms of Nonpharmacologic Interventions in TRD Populations (Tier 1)

Direct Evidence

In examining safety, adverse events, and adherence, we found some differences across the interventions in the harms and negative side effects to patients, however the data were insufficient to reach a conclusive result. For just this set of analyses, we examined both trials and cohort studies, and we focus on cognitive functioning, occurrence of specific adverse events, and withdrawals.

Cognitive Functioning

For Tier 1 studies on cognitive functioning, some evidence suggests no differences in changes in cognitive functioning between groups, while some evidence suggests ECT may have a deleterious impact on cognitive functioning compared to rTMS (insufficient strength of evidence).

No differences between groups on a single item measure of cognitive functioning were found in a study comparing ECT with ECT and rTMS (insufficient strength of evidence).

Specific Adverse Events

One Tier 1 study comparing ECT with a combination of ECT and rTMS found no differences in specific adverse events (low strength of evidence).

Withdrawals

We looked at both withdrawals that investigators attributed to adverse events and overall numbers or rates of withdrawals. A single study with a small sample size indicated no difference in withdrawals due to adverse events for the ECT group when compared to rTMS but did not report on the significance of this result (low strength of evidence).

Evidence for ECT compared with rTMS indicated higher rates of overall withdrawals in the ECT compared to the rTMS group ($P = NR$; low strength of evidence).

Indirect Evidence

We attempted to include data from the same types of studies and for the same outcomes as for direct evidence. We identified no studies comparing ECT versus control.

Cognitive Functioning

Mixed evidence on cognitive functioning in rTMS versus sham was insufficient to draw a conclusion (insufficient strength of evidence).

Specific Adverse Events

rTMS groups reported significantly more scalp pain at the stimulation site (low strength of evidence).

Some differences in the frequency of specific adverse events were seen when comparing VNS and sham groups, but the significance of the findings was not reported (low strength of evidence).

Withdrawals

Findings were mixed in Tier 1 studies as to whether rTMS groups had greater rates of withdrawals due to adverse events and overall withdrawals than groups receiving sham procedures (insufficient evidence for both).

There was low strength of evidence that there were greater withdrawals due to adverse events in the vagus nerve stimulation group compared to sham.

No Tier 1 studies reported on withdrawals for CBT groups versus those receiving some form of usual care.

KQ 5. Efficacy or Harms of Nonpharmacologic Treatments for Selected Patient Subgroups in TRD Populations (Tier 1)

Direct Evidence

We found no studies (in any tier) directly comparing nonpharmacologic interventions in selected populations, such as the elderly, those with stroke, or those with other medical comorbidities.

Indirect Evidence

Three Tier 1 trials compared rTMS versus sham. A single trial, each, found that rTMS produced a greater decrease in depressive severity than sham for young adults (ages 18–37) and in older adults with post-stroke depression (both low strength of evidence). A single trial in young adults indicated that rTMS produces a greater response rate than sham in young adults (ages 18–37) (low strength of evidence), while a single study identified no difference in response rates between rTMS and sham in older adults with post-stroke depression (low strength of evidence). Finally, a single study found no difference in remission rates for rTMS versus sham in older adults with post-stroke depression.

KQ 6. Health-Related Outcomes of Nonpharmacologic Treatments in TRD Populations (Tier 1)

Direct Evidence

With respect to patient-reported health-related outcomes, we focused on quality of life (various measures) and ability to function in daily life. One Tier 1 study compared ECT with a combination of ECT and rTMS and found no differences between groups in improvement on the Global Assessment of Functioning scale (low strength of evidence).

Indirect Evidence

Two trials (both in mixed MDD/bipolar populations) assessed general health status and mental and physical functioning (all health domains related to quality of life). In one fair trial, low rTMS had significantly greater improvement in health status and daily functioning than sham, while this relationship approached statistical significance when comparing high rTMS to sham (as measured by the Global Assessment of Functioning scale; low strength of evidence). In the other fair trial, VNS and sham groups did not differ significantly in daily functioning (as measured by the 36-item Medical Outcomes Study Short Form [MOS SF-36]; low strength of evidence). No studies of psychotherapy were identified.

Applicability

For the limited amount and low strength of evidence available, the data for Tier 1 (TRD) is generally applicable to TRD populations. Populations enrolled in these trials appeared representative of our target population. Studied interventions were comparable to those in routine use, though dose and duration of nonpharmacologic treatment often varied between studies. Measured outcomes on the whole reflected the most important clinical outcomes for depression measures, although reporting was inconsistent; outcomes for the other key questions were much more restricted. Followup periods were generally shorter than desirable, but most were sufficient to measure an initial acute-phase treatment response. Study settings were a mixture of inpatient and outpatient. Some evidence highlights the importance of patient acceptability of treatment as some patients refuse particular interventions. An individualized balance between patient's needs and concerns must be taken into account during selection from a range of nonpharmacologic and pharmacologic antidepressant treatment options. The use of varying definitions of TRD in the trials and the absence of analyses considering the effect of the number of current episode treatment failures on outcomes hindered interpretation of data, leading to the use of a tiered system. The evidence base combining data for Tiers 1–3 on the whole produced findings that were consistent with Tier 1 TRD data and also appear applicable to TRD populations.

Limitations of the Evidence Base

Lack of use of a Standard Definition of TRD

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by variable definitions of TRD. Although these definitions appear to be consolidating towards a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it. Use of multiple definitions makes synthesis of the available information difficult, as the effect of combining patients with one treatment failure with those of two or more (or four or more) remains unclear.

Similarly, the failure of studies to describe the number of treatment failures prevented us from being able to stratify our outcomes by the number of failed trials within Tier 1 studies and assess the role of number of failures in TRD on outcomes.

Ultimately, TRD is a complex phenomenon that encompasses the number of treatment failures, the adequacy of prior treatments, depressive severity, comorbidities (both psychiatric and medical), symptom subtypes, and chronicity. The currently available evidence base has yet to successfully and consistently apply a standard definition.

Failure to Consistently Assess Number of Failures in Current Episode

Given the difficulty in accurately assessing adequacy of prior treatment trials over a lifetime, a history of failed treatment attempts in a current episode is likely a more accurate measure of treatment resistance. It is likely that many of those who reported lifetime histories of two or more failures did have them in the current episode, but few studies required such a failure in their selection criteria; many studies may be mixing current failure with more chronic failures.

Few Head-to-Head Studies of Nonpharmacologic Intervention

The small number of existing head-to-head studies limits the strength of all our findings to either low or insufficient evidence, making firm conclusions about comparative effectiveness

impossible. Only two studies occurred in our main population of interest: patients with MDD who had two or more antidepressant failures.^{58,64}

Heterogeneity of the Populations (MDD and MDD/Bipolar mix)

This mixture of diagnostic disorders in samples made interpretation of the data difficult. Populations studied included MDD and MDD/bipolar mix patients. We selected a 20 percent cutoff to decrease the likelihood of the mix affecting outcomes (e.g., in a study of 40 patients, if 8 had bipolar disorder and were roughly evenly distributed between treatment arms, their outcomes would need to be extreme to substantially affect outcome). This need to clarify a specific cutoff, however, excluded studies that may have had relevant populations. Further, because results were not stratified by MDD and bipolar disease, the precision of the effect on the nonpharmacologic outcomes may have been distorted.

Failure to Consider a Spectrum of Depressive Severity

Most patients involved in studies were severely depressed and analyses did not assess how the degree of depression along the severity spectrum may affect outcomes in comparative studies. For example, the most severely depressed may have different outcomes with one versus another intervention than those who are severely depressed but to a lesser degree.

Heterogeneity of Interventions and Intervention Strategies

The literature is characterized by a large variety of treatment strategies used (augmentation, switch, a combination of the two), a wide variety of treatment parameters used (length and dose of ECT, number of rTMS sessions), and variable and uncontrolled use of psychotropic medications, all of which make interpretation and synthesis of the studies difficult.

Limited outcome elements assessed. Although they reported one or two of the pertinent outcomes, the majority of the relevant studies did not assess both response and remission rates. These measures are especially important to allow a clinically meaningful interpretation of findings.

Few Comparisons of Nonpharmacologic to Pharmacologic Treatments in TRD Patients

For many clinicians, the next step following failure of two antidepressant treatments is not consideration of a nonpharmacologic treatment but usually consideration of a different pharmacologic strategy. The role of nonpharmacologic interventions in the sequence of treatment choices remains unclear.

Difficulty in Identifying a Reasonable Sham Control Group for Device-Related Studies

Challenges in finding an appropriate sham arm may have distorted results from the intervention-control comparisons. Because of the need for general anesthesia, “sham ECT” has proven ethically problematic over the years. Given the noninvasive nature of rTMS, there is much objection to the use of a sham control condition, in which the electrode would be placed against the scalp but the magnetic stimulation not applied. The problem is that a completely “inert” sham condition experience may not be credible to patients who are aware of the noise and vibration that typically accompanies active rTMS.^{53,139} Similarly, the limited number of reported

VNS studies identified have come under similar criticism for the apparently transparent nature of the control condition.¹⁴⁰

Inadequate Study Design to Assess Longer Term Outcomes

Studies need to have more long-term monitoring over time so that the outcomes can be further studied. For example, the available studies for ECT did not follow patients long enough to assess potential cumulative effects on cognitive functioning that may distinguish it from other interventions. Additionally, longer monitoring periods are necessary to compare the maintenance of remission.

Studies Were not Designed to Answer Many of the Outcomes Relevant to the KQ

Outcomes such as relapse, cognitive functioning, adverse events, withdrawal due to adverse events, and health-related outcomes are not often primary outcomes, limiting the power to adequately test hypotheses about such differences between nonpharmacologic interventions.

Absence of Psychotherapy Studies Involving a TRD Population

Although some Tier 2 and 3 studies involved psychotherapy, there were no studies addressing a Tier 1 population (TRD). Also, no studies from any tiers involved interpersonal therapy. While there are a variety of reasons that make clinical trials involving psychotherapy challenging (e.g., treatments are often not widely available outside research centers, and both patients and clinicians often view these studies as underpowered or the research protocol as too complicated for application in practice settings), such research would be quite informative for decisionmakers.

These Treatments are Quite Different

Differences in these interventions—how long it takes to reach an adequate dose, how effectively patients can be blinded, how long it takes to obtain a response, how long the results last—make it challenging to directly compare these varying treatments. For example, with ECT, if there is no effect in 2 weeks, one might consider switching treatments, whereas with CBT, such a latency would not be a cause for concern.

Limitations of This Review

This area of comparative clinical research is in its infancy, and few relevant trials were available. The paucity of data limited our ability to pool findings statistically. Specifically, we were not able to quantitatively synthesize data from head-to-head comparisons, nor were we able to indirectly compare the nonpharmacologic literature by pooling data from studies sharing equivalent control groups. Our synthesis, then, is primarily qualitative.

The dearth of relevant trials also prevented us from assessing whether key elements might suggest one nonpharmacologic treatment over another. In particular, we were unable to assess what the effect on outcome was of key, clinically relevant elements of interest: population variables (MDD and MDD/bipolar mix; varying depressive severity; and requiring treatment failures to be in the current episode) and intervention variables (using an augmentation versus switch treatment strategy; varying by nonpharmacologic treatment characteristics).

Future Research

This area of comparative clinical research is in its infancy. Key areas for future research need primarily to lay more robust foundations for an evidence base that can better inform decisions for clinicians and patients.

The Field Needs a Standard Definition of TRD That Investigators Should use in Their Clinical Trials Research

Comparison of any of the potential interventions in the field, nonpharmacologic or otherwise, is hampered by the variability in TRD definitions. Although these definitions appear to be converging on a single meaning—two or more treatment failures in the current episode—very few studies of TRD have applied it. Progress in this area of research requires better standardization of this concept, so that future reviews of the evidence do not need to resort to differentiating, as we did, between “Tier 1” studies (i.e., TRD by this definition based on two or more treatment failures) and “Tier 2 or 3” types of studies. The latter do provide information that helps illuminate likely impacts of these interventions on patients with TRD, but that is not the same thing as having robust studies focused clearly on the patient population of greatest interest. The challenge will be to provide a definition that operationalizes TRD to make it feasible for clinicians while at the same time successfully capturing the complexity of treatment resistance.

More Clinical Trials, as Well as Other Possible Study Designs, That Compare Nonpharmacologic Interventions With Other Nonpharmacologic Options and With Pharmacologic Treatments are Necessary to Inform Decisionmaking in TRD

Clinicians, patients, and policymakers need additional relevant data to guide difficult treatment decisions about what to do next: try another medication trial (and should it be an augmentation, switch, or combination strategy?); add (or switch to) rTMS, ECT, VNS, or psychotherapy?

Also, given that treatment options for many TRD patients include medications, trials should directly compare nonpharmacologic interventions with each other and with pharmacologic treatments.

The Number of Treatment Failures in the Current Episode Should be Delineated Carefully

This information, more likely to be accurate than lifetime histories of failures, can help investigators determine whether the particular number of failures, or reaching a particular number of failures in a current episode, can help differentiate between nonpharmacologic treatment choices. For example, for patients with two failures in a current episode, the outcomes may not differ between cognitive therapy and rTMS; however, for patients with a different (higher or lower) number of failures in the current episode, one nonpharmacologic treatment may indeed be better than the other. Currently, we do not know what the proper threshold is for selection of treatment. Clarification of the scientific basis for such a decision would substantially improve decisionmaking.

Clarifying Whether Responses Differ for TRD Patients With MDD Compared to Those With Bipolar Disorder Will Help to Guide Future Clinical Trial Design

Our decision to include trials with patient populations including up to 20 percent with bipolar disorder (i.e., the “mixed” populations noted earlier) was guided by clinical experience and common sense but not by data. Testing to see whether outcomes differ between the two groups can yield information about inclusion criteria (should the mix be 0%, 10%, 20%, etc.?) that may be useful to investigators in designing TRD trials and may be important to consider as a potential covariate in analyses involving such mixes.

Greater Consideration Should be Given to the Role That the Spectrum of Depressive Severity Plays

Using a finer gradation of depressive severity than investigators now typically employ might identify whether particularly severe degrees of depression, most commonly understood currently as a $\text{HAM-D}_{17} \geq 20$, may respond differently to the available nonpharmacologic interventions than do less severe levels of depression. These gradations may lead clinicians to a better understanding of severe depression and its role in guiding treatment selection in TRD.

Direct Comparisons of Treatment Strategies, Holding Consistent any Coexisting or Concomitant Therapies, are Imperative

Decisionmakers need to know whether outcomes with nonpharmacologic treatments are better when such a treatment augments the current treatment, replaces the current treatment, or replaces the current treatment in combination with another treatment. When ongoing treatment is uncontrolled and reflects a variety of treatments—e.g., some patients continue with atypical antipsychotics, some with mood stabilizers, some with no psychotropic medications—results of such studies are difficult, if not impossible, to interpret.

Consistent Reporting of Changes in Depressive Severity, Response Rates, and Remission Rates is Crucial

To allow for better comparisons of clinical outcomes in this difficult-to-treat population, all three measures offer useful information for clinicians. Thus, for either trials or observational studies, investigators should attempt to collect data on all three routinely.

Application of Consistent, Accepted Protocols in Trials is Necessary

Making sure that patients receive equivalent doses of different nonpharmacologic interventions is more difficult than making sure of this for pharmacologic interventions. Nevertheless, investigators designing trials of nonpharmacologic therapies can attempt to do so by implementing standard accepted protocols for their trials. Such “dosing” had been difficult to control when that protocol was in the process of being developed, as with rTMS, but given current treatment parameters, this standardization is a goal well worth trying to reach.

More Careful and Consistent Assessment of Adverse Events is Required

Adverse event reporting is quite limited and over a short timespan, and what exists is variable and inconsistent. Systematic collection and more consistent reporting of data on harms—i.e., adverse events and negative side effects—and information about attrition and withdrawal would provide useful information to help balance information now focused on clinical benefits. Use of the CONSORT (Consolidated Standards of Reporting Trials) statement (available at: <http://www.consort-statement.org/home/>), which guides proper reporting of study information (including the presentation of adverse events), would strengthen reporting both harms and other clinical trial findings; it would also aid in the critical appraisal and interpretation of all study results. Further, a more informative assessment of adverse events would require studies to be able to assess long-term and cumulative outcomes.

Including key Relevant Measures and Subgroups in Subsequent Research is Desirable

As indicated by the review, nearly no evidence exists on how the effectiveness of nonpharmacologic treatments differs (or not) as a function of symptom subtypes or for subgroups defined by sociodemographic characteristic (such as age) or coexisting medical conditions (e.g., post-stroke or postmyocardial infarction depression; perinatal depression). Also essentially missing is information about health-related outcomes, especially those reported by patients, that concern their quality of life or levels of functional impairment. Subsequent studies should focus on employing known, reliable, and valid measures of patient-reported outcomes, such as the MOS SF-36,¹⁴¹ the Quality of Life Enjoyment and Satisfaction Questionnaire (Q-LES-Q),¹³⁵ and the EQ-5D.¹⁴²

Including Comparisons of Newer Nonpharmacologic Interventions Will be Important in Future Research

As new nonpharmacologic treatments are developed and tested, investigators should try to include them as potential comparators. At the time we started this comparative effectiveness review, clinical trial data on some of the developing nonpharmacologic interventions, such as magnetic seizure therapy,¹⁴³⁻¹⁴⁵ deep brain stimulation,¹⁴⁶⁻¹⁴⁸ or mindfulness-based cognitive therapy¹⁴⁹ were insufficient (from the published literature) for us to try to include them. As the evidence bases grow to support the efficacy of such additional nonpharmacologic interventions, the newer strategies should be included in comparative effectiveness study designs.

Conclusion

Our review suggests that comparative clinical research on nonpharmacologic interventions in a TRD population is in its infancy, and many clinical questions about efficacy and effectiveness remain unanswered. Interpretation of the data is substantially hindered by varying definitions of TRD and the paucity of relevant studies. The greatest volume of evidence is for ECT and rTMS; however, even for the few comparisons of treatments that are supported by some evidence, the strength of evidence is low for comparative benefits. Specifically, there was low strength of evidence that ECT and rTMS did not produce different clinical outcomes in TRD, and low strength of evidence that ECT produced better outcomes than pharmacotherapy. No trials

directly compared the likelihood of maintaining remission for nonpharmacologic interventions. The few trials addressing adverse events, subpopulations, subtypes, and health-related outcomes provided low or insufficient evidence of differences between nonpharmacologic interventions. The most urgent next steps for research are to apply a consistent definition of TRD, to conduct more head-to-head clinical trials comparing nonpharmacologic interventions to one another and to pharmacologic treatments, and to carefully delineate the number of adequate treatment failures in the current episode.

References

1. Kessler RC, Berglund P, Demler O, et al. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). *JAMA*. 2003 Jun 18;289(23):3095-3105. PMID: 12813115.
2. Wang PS, Lane M, Olfson M, et al. Twelve-month use of mental health services in the United States: results from the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005 Jun;62(6):629-40. PMID: 15939840.
3. American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). *American Journal of Psychiatry* 2000 Apr;157(4 Suppl):1-45. PMID: 10767867.
4. Qaseem A, Snow V, Denberg TD, et al. Using second-generation antidepressants to treat depressive disorders: a clinical practice guideline from the American College of Physicians. *Ann Intern Med* 2008 Nov 18;149(10):725-33. PMID: 19017591.
5. Kupfer DJ. Long-term treatment of depression. *J Clin Psychiatry* 1991 May;52 Suppl:28-34. PMID: 1903134.
6. Trivedi MH, Rush AJ, Wisniewski SR, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006 Jan;163(1):28-40. PMID: 16390886.
7. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry* 1997;58 Suppl 13:23-9. PMID: 9402916.
8. Rush AJ, Trivedi MH, Wisniewski SR, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry* 2006;163(11):1905-17. PMID: 16390886.
9. Berlim MT, Fleck MP, Turecki G. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. *Ann Med* 2008;40(2):149-59. PMID: 18293145.
10. Thase ME. New approaches to managing difficult-to-treat depressions. *The J Clin Psychiatry* 2003;64:3-4.
11. Russell JM, Hawkins K, Ozminkowski RJ, et al. The cost consequences of treatment-resistant depression. *J Clin Psychiatry* 2004 Mar;65(3):341-7. PMID: 15096073.
12. Crown WH, Finkelstein S, Berndt ER, et al. The impact of treatment-resistant depression on health care utilization and costs. *J Clin Psychiatry* 2002 Nov;63(11):963-71. PMID: 12444808.
13. Greenberg P, Corey-Lisle PK, Birnbaum H, et al. Economic implications of treatment-resistant depression among employees. *Pharmacoeconomics* 2004;22(6):363-73. PMID: 15099122.
14. Gartlehner G, Gaynes BN, Hansen RA, et al. Comparative benefits and harms of second-generation antidepressants: background paper for the American College of Physicians. *Ann Intern Med* 2008 Nov 18;149(10):734-50. PMID: 19017592.
15. Tharyan P. The Cochrane Schizophrenia Group: preparing, maintaining and disseminating the evidence for interventions used for people with schizophrenia. *Int Rev Psychiatry* 2005 Apr;17(2):115-21. PMID: 16194781.
16. Greenhalgh J, Knight C, Hind D, et al. Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies. *Health Technol Assess* 2005 Mar;9(9):1-156, iii-iv. PMID: 15774232.
17. Lisanby SH. Electroconvulsive therapy for depression. *N Engl J Med* 2007 Nov 8;357(19):1939-45. PMID: 17989386.

18. Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006 Jan;163(1):88-94. PMID: 16390894.
19. Feldman G. Cognitive and behavioral therapies for depression: overview, new directions, and practical recommendations for dissemination. *Psychiatr Clin North Am* 2007 Mar;30(1):39-50. PMID: 17362802.
20. Schramm E, van Calker D, Dykieriek P, et al. An intensive treatment program of interpersonal psychotherapy plus pharmacotherapy for depressed inpatients: acute and long-term results. *Am J Psychiatry* 2007 May;164(5):768-77. PMID: 17475736.
21. George MS, Belmaker RH, eds. *Transcranial magnetic stimulation in clinical psychiatry*. Arlington, VA: American Psychiatric Publishing 2007.
22. Shapira B, Tubi N, Lerer B. Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J Ect* 2000 Jun;16(2):97-109. PMID: 10868320.
23. Rossi S, Hallett M, Rossini PM, et al. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009 Dec;120(12):2008-39. PMID: 19833552.
24. Daban C, Martinez-Aran A, Cruz N, et al. Safety and efficacy of Vagus Nerve Stimulation in treatment-resistant depression. A systematic review. *J Affect Disord* 2008 Sep;110(1-2):1-15. PMID: 18374988.
25. Neuronetics. *NeuroStar TMS System™ User Manual*. 2006.
26. Lisanby SH, Pallanti S, Schlaepfer TE. FDA considers classification of ECT. *CNS Spectrums* 2009;14(12):668-70. PMID:
27. Centers for Medicare & Medicaid Services. *Update-Inpatient Psychiatric Facilities Prospective Payment System (IPF PPS). Rate Year 2009, Publication # 100-04; 2008 June 27*.
28. Patel M, Patel S, Hardy DW, et al. Should electroconvulsive therapy be an early consideration for suicidal patients? *J ECT* 2006 Jun;22(2):113-5. PMID: 16801826.
29. Tew JD, Jr., Mulsant BH, Haskett RF, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. *Am J Psychiatry* 1999 Dec;156(12):1865-70. PMID: 10588398.
30. Van Der Wurff FB, Stek ML, Hoogendijk WJ, et al. The efficacy and safety of ECT in depressed older adults: a literature review (Brief record). *International Journal of Geriatric Psychiatry* 2003(10):894-904. PMID: 14533122 DARE-12003006812.
31. Walter G, Martin J, Kirkby K, et al. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Aust N Z J Psychiatry* 2001 Feb;35(1):58-61. PMID: 11270457.
32. Simpson KN, Welch MJ, Kozel FA, et al. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. *Adv Ther* 2009 Mar;26(3):346-68. PMID: 19330495.
33. Marangell LB, Martinez M, Jurdi RA, et al. Neurostimulation therapies in depression: a review of new modalities. *Acta Psychiatr Scand* 2007 Sep;116(3):174-81. PMID: 17655558.
34. Melkerson MN. Special Premarket 510(k) Notification for NeuroStar TMS Therapy System for Major Depressive Disorder. 2008. Available at: http://www.accessdata.fda.gov/cdrh_docs/pdf8/K083538.pdf.
35. Belmaker B, Fitzgerald P, George MS, et al. Managing the risks of repetitive transcranial stimulation. *CNS Spectrums* 2003;8(7). PMID:
36. Shuchman M. Approving the vagus-nerve stimulator for depression. *N Engl J Med* 2007;356(16):1604-7. PMID:
37. Lulic D, Ahmadian A, Baaj AA, et al. Vagus nerve stimulation. *Neurosurg Focus* 2009 Sep;27(3):E5. PMID: 19722820.
38. Federal Drug Administration. *Summary of Safety and Effectiveness Data: Stimulator, Vagus Nerve*. 20051-23.

39. Cohen LJ, Allen JC, Jr. Estimating the potential savings with vagus nerve stimulation for treatment-resistant depression: a payer perspective. *Curr Med Res Opin* 2008 Aug;24(8):2203-17. PMID: 18786301.
40. Rush AJ, Siefert SE. Clinical issues in considering vagus nerve stimulation for treatment-resistant depression. *Exp Neurol* 2009 Sep;219(1):36-43. PMID: 19397908.
41. Rush AJ, Sackeim HA, Marangell LB, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry* 2005 Sep 1;58(5):355-63. PMID: 16139581.
42. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 2005 Sep 1;58(5):364-73. PMID: 16139582.
43. Luty SE, Carter JD, McKenzie JM, et al. Randomised controlled trial of interpersonal psychotherapy and cognitive-behavioural therapy for depression. *Br J Psychiatry* 2007 Jun;190:496-502. PMID: 17541109.
44. Bortolotti B, Menchetti M, Bellini F, et al. Psychological interventions for major depression in primary care: a meta-analytic review of randomized controlled trials. *Gen Hosp Psychiatry* 2008 Jul-Aug;30(4):293-302. PMID: 18585531.
45. Butler AC, Chapman JE, Forman EM, et al. The empirical status of cognitive-behavioral therapy: a review of meta-analyses. *Clin Psychol Rev* 2006 Jan;26(1):17-31. PMID: 16199119.
46. DeRubeis RJ, Hollon SD, Amsterdam JD, et al. Cognitive therapy vs medications in the treatment of moderate to severe depression. *Arch Gen Psychiatry* 2005 Apr;62(4):409-16. PMID: 15809408.
47. Shelton RC, Osuntokun O, Heinloth AN, et al. Therapeutic options for treatment-resistant depression. *CNS Drugs* 2010 Feb 1;24(2):131-61. PMID: 20088620.
48. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol* 2007 Nov;17(11):696-707. PMID: 17521891.
49. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry* 2007 Jan;52(1):46-54. PMID: 17444078.
50. Fornaro M, Giosue P. Current nosology of treatment resistant depression: a controversy resistant to revision. *Clin Pract Epidemiol Ment Health* 2010;6:20-4. PMID: 20563286.
51. Malhi GS, Parker GB, Crawford J, et al. Treatment-resistant depression: resistant to definition? *Acta Psychiatr Scand* 2005 Oct;112(4):302-9. PMID: 16156838.
52. Goldberg DP, Andrews G, Hobbs MJ. Where should bipolar disorder appear in the meta-structure? *Psychological Medicine* 2009;39(12):2071-81. PMID:
53. Lisanby SH, Gutman D, Luber B, et al. Sham TMS: intracerebral measurement of the induced electrical field and the induction of motor-evoked potentials. *Biol Psychiatry* 2001 Mar 1;49(5):460-3. PMID: 11274658.
54. Loo CK, Taylor JL, Gandevia SC, et al. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biol Psychiatry* 2004;47(4):325-31.
55. Inventory of Depressive Symptomatology (IDS) and Quick Inventory of Depressive Symptomatology (QIDS). University of Pittsburgh Epidemiology Data Center 2010. Available at: <http://www.ids-qids.org/index2.html>.
56. Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions--Agency for Healthcare Research and Quality and the Effective Health Care Program. *Journal of Clinical Epidemiology* 2010;63(5):513-23. PMID:

57. Agency for Healthcare Research and Quality. Methods Reference Guide for Effectiveness and Comparative Effectiveness Reviews. Version 1.0 [Draft posted Oct. 2007]. Rockville, MD. Available at: http://effectivehealthcare.ahrq.gov/repFiles/2007_10DraftMethodsGuide.pdf.
58. Rosa MA, Gattaz WF, Pascual-Leone A, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol* 2006 Dec;9(6):667-76. PMID: 16923322.
59. Grunhaus L, Schreiber S, Dolberg OT, et al. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003 Feb 15;53(4):324-31. PMID: 12586451.
60. Hansen PE, Ravnkilde B, Videbech P, et al. Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. *J ECT* 2010 Mar 25. PMID: 20351570.
61. McLoughlin DM, Mogg A, Eranti S, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess* 2007 Jul;11(24):1-54. PMID: 17580003.
62. Eranti S, Mogg A, Pluck G, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry* 2007 Jan;164(1):73-81. PMID: 17202547.
63. Knapp M, Romeo R, Mogg A, et al. Cost-effectiveness of transcranial magnetic stimulation vs electroconvulsive therapy for severe depression: A multi-centre randomised controlled trial. *Journal of Affective Disorders* 2008 Aug 2008;109(3):273-85. PMID: 18262655.
64. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety* 2000;12(3):118-23. PMID: 11126185.
65. Chistyakov AV, Kaplan B, Rubichek O, et al. Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clin Neurophysiol* 2005 Feb;116(2):386-92. PMID: 15661116.
66. Folkerts HW, Michael N, Tölle R, et al. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. *Acta Psychiatr Scand* 1997 Nov;96(5):334-42. PMID: 9395150.
67. West ED. Electric convulsion therapy in depression: a double-blind controlled trial. *Br Med J (Clin Res Ed)* 1981;282(6261):355-7. PMID: 6780021.
68. Johnstone EC, Deakin JF, Lawler P, et al. The Northwick Park electroconvulsive therapy trial. *Lancet* 1980;2(8208-8209):1317-20. PMID: 6109147.
69. Boutros NN, Gueorguieva R, Hoffman RE, et al. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Research* 2002 Dec 2002;113(3):245-54. PMID: 12559481.
70. Garcia-Toro M, Mayol A, Arnillas H, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders* 2001 May 2001;64(2):271-5. PMID: 11313095.
71. Garcia-Toro M, Salva J, Daumal J, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res* 2006 Jan 30;146(1):53-7. PMID: 16356697.
72. Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression and Anxiety* 2004;19(1):59-62. PMID: 14978787.

73. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;88(3):163-71. PMID: 10622338.
74. Pallanti S, Bernardi S, Di Rollo A, et al. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience* 2010;167(2):323-8. PMID: 20144692.
75. Zheng H, Zhang L, Li L, et al. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 2010;34(7):1189-95. PMID: 20600472. First Author & Affiliation: Zheng, Huirong.
76. Holtzheimer PE, 3rd, Russo J, Claypoole KH, et al. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety* 2004;19(1):24-30. PMID: 14978782.
77. Avery DH, Holtzheimer PE, 3rd, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry* 2006 Jan 15;59(2):187-94. PMID: 16139808.
78. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet* 1996 Jul 27;348(9022):233-7. PMID: 8684201.
79. Bocchio-Chiavetto L, Miniussi C, Zanardini R, et al. 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug resistant depression. *Neurosci Lett* 2008 May 30;437(2):130-4. PMID: 18450378.
80. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003 Oct;60(10):1002-8. PMID: 14557145.
81. Su T-P, Huang C-C, Wei IH. Add-On rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry* 2005 Jul 2005;66(7):930-7. PMID: 16013911.
82. Triggs WJ, Ricciuti N, Ward HE, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res* 2010;178(3):467-74. PMID: 20643486.
83. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010 May;67(5):507-16. PMID: 20439832.
84. Manes F, Jorge R, Morcuende M, et al. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics* 2001 Jun 2001;13(2):225-31. PMID: 11495396.
85. Moser DJ, Jorge RE, Manes F, et al. Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology* 2002;58(8):1288-90. PMID: 11971103.
86. Stern WM, Tormos JM, Press DZ, et al. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci* 2007 Spring;19(2):179-86. PMID: 17431065.
87. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;62(11):1208-16. PMID: 17573044.
88. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry* 2000 Feb 2000;47(4):332-7. PMID: 10686268.

89. Bretlau LG, Lunde M, Lindberg L, et al. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry* 2008 Mar;41(2):41-7. PMID: 18311683.
90. Bortolomasi M, Minelli A, Fuggetta G, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res* 2007 Mar 30;150(2):181-6. PMID: 17303249.
91. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry* 1997 Dec;154(12):1752-6. PMID: 9396958.
92. Möller AL, Hjaltason Ó, Ívarsson Ó, et al. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P-sub-3-sub-0-sub-0 event-related potential. *Nordic Journal of Psychiatry* 2006;60(4):282-5. PMID: 16923636.
93. Harley R, Sprich S, Safren S, et al. Adaptation of dialectical behavior therapy skills training group for treatment-resistant depression. *J Nerv Ment Dis* 2008 Feb;196(2):136-43. PMID: 18277222.
94. Kocsis JH, Gelenberg AJ, Rothbaum BO, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: The REVAMP trial. *Archives of General Psychiatry* 2009;66(11):1178-88. PMID: 19884606. First Author & Affiliation: Kocsis, James H.
95. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. A controlled trial. *Archives of General Psychiatry* 1999;56(9):829-35. PMID:
96. Scott J, Teasdale JD, Paykel ES, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual. *British Journal of Psychiatry* 2000;177(NOV.):440-6. PMID:
97. Wiles NJ, Hollinghurst S, Mason V, et al. A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: A pilot study. *Behavioural and Cognitive Psychotherapy* 2008 Jan 2008;36(1):21-33.
98. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry* 2005 Sep 2005;58(5):347-54. PMID: 16139580.
99. Avery DH, Holtzheimer PE, 3rd, Fawaz W, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis* 2007 May;195(5):378-81. PMID: 17502802.
100. Moller AL, Hjaltason O, Ivarsson O, et al. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P(300) event-related potential. *Nord J Psychiatry* 2006;60(4):282-5. PMID: 16923636.
101. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* 2007;164(5):739-52. PMID: 17475733.
102. Moore RG, Blackburn I-M. Cognitive therapy in the treatment of non-responders to antidepressant medication: A controlled pilot study. *Behavioural and Cognitive Psychotherapy* 1997 1997;25(3):251-9.
103. Corya SA, Williamson D, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety* 2006;23(6):364-72. PMID: 16710853.
104. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry* 2006;163(7):1161-72. PMID: 16816220.

105. Mazeh D, Shahal B, Aviv A, et al. A randomized, single-blind, comparison of venlafaxine with paroxetine in elderly patients suffering from resistant depression. *Int Clin Psychopharmacol* 2007;22(6):371-5. PMID: 17917556.
106. McGrath PJ, Stewart JW, Fava M, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry* 2006;163(9):1531-41; quiz 666. PMID: 16946177.
107. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomized comparison. *Br J Psychiatry* 1999;175:12-6. PMID: 10621762.
108. Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry* 2005;66(10):1289-97. PMID: 16259543.
109. Nierenberg AA, Papakostas GI, Petersen T, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. *Journal of Clinical Psychopharmacology* 2003;23(1):92-5. PMID: 12544380.
110. Shelton RC, Tollefson GD, Tohen M, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry* 2001;158(1):131-4. PMID: 11136647.
111. Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry* 2007;68(2):224-36. PMID: 17335320.
112. Fang Y, Yuan C, Xu Y, et al. Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: A double-blind, randomized pilot study in a Chinese population. *Journal of Clinical Psychopharmacology* 2010;30(4):357-64. PMID: 20571433. First Author & Affiliation: Fang, Yiru.
113. Berman, RM, Marcus, RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder : A multicenter, randomized, double-blind, placebo-controlled study. *J Clin Psychiatry* 2007;68(6):843-853. PMID: 17592907
114. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr* 2009;14(4):197-206. PMID: 19407731.
115. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of acute response to TMS in the treatment of major depression: relapse during a continuation pharmacotherapy extension study. *Society of Biological Psychiatry Annual Meeting; 2007 May; San Diego, CA; 2007.*
116. Solvason HB, Husain M, Fitzgerald PB, et al. TMS in the acute treatment of major depression: Improvements in functional status and quality of life. *Society of Biological Psychiatry Annual Meeting; 2007 May; San Diego, CA; 2007.*
117. Dannon PN, Dolberg OT, Schreiber S, et al. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals--preliminary report. *Biol Psychiatry* 2002 Apr 15;51(8):687-90. PMID: 11955470.
118. Grunhaus L, Dannon PN, Schreiber S, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry* 2000 Feb 15;47(4):314-24. PMID: 10686266.
119. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation* 2010;3(4):187-99. PMID: 20965447. First Author & Affiliation: Janicak, Philip G.

120. Scott J, Palmer S, Paykel E, et al. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. *Br J Psychiatry* 2003 Mar;182:221-7. PMID: 12611785.
121. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. *Psychol Med* 2005;35(1):59-68. PMID: 15842029.
122. Dannon PN, Schreiber S, Dolberg OT, et al. Transcranial magnetic stimulation is effective in the treatment of relapse of depression. *International Journal of Psychiatry in Clinical Practice* 2000;4(3):223-6. PMID:
123. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, et al. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry* 2005 May;186:410-6. PMID: 15863746.
124. Demitrack MA, Loo CK, Maixner DF, et al. Transcranial Magnetic Stimulatlin (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment. Society for Biological Psychiatry Annual Meeting and New Research Sessions of the American Psychiatric Association Annual Meeting; 2009 May; Vancouver B.C., San Francisco, CA; 2009.
125. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry* 2008;69(2):222-32. PMID: 18232722.
126. O'Connor M, Brennkinkmeyer C, Morgan A, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. *Cogn Behav Neurol* 2003 Jun;16(2):118-27. PMID: 12799598.
127. Frith CD, Stevens M, Johnstone EC, et al. Effects of ECT and depression on various aspects of memory. *Br J Psychiatry* 1983;142:610-7. PMID: 6882984.
128. Frith CD, Stevens M, Johnstone EC, et al. A comparison of some retrograde and anterograde effects of electroconvulsive shock in patients with severe depression. *Br J Psychol* 1987;78 (Pt 1):53-63. PMID: 3828659.
129. Jorge RE, Moser DJ, Acion L, et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry* 2008 Mar;65(3):268-76. PMID: 18316673.
130. Jorge RE, Robinson RG, Tateno A, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry* 2004 Feb 15;55(4):398-405. PMID: 14960293.
131. Aas IH. Global assessment of functioning (GAF): properties and frontier of current knowledge. *Ann Gen Psychiatry* 2010;9(1):20.
132. Leon AC, Solomon DA, Mueller TI, et al. The range of impaired functioning tool (LIFE-RIFT): a brief measure of functional impairment. *Psychol Med* 1999;29(4):869-78.
133. Ware JE, Snow KK, Kosinski M, et al. SF-36 Health Survey manual and interpretation guide. Boston, MA: The Health Institute, New England Medical Centre; 1993.
134. Wisniewski SR, Rush AJ, Bryan C, et al. Comparison of quality of life measures in a depressed population. *The Journal of Nervous and Mental Disease* 2007;195(3):219-25.
135. Endicott J, Nee J, Harrison W, et al. Quality of Life Enjoyment and Satisfaction Questionnaire: A New Measure. 1993.
136. Achard S, Chignon JM, Poirier-Littre MF, et al. Social adjustment and depression: value of the SAS-SR (Social Adjustment Scale Self-Report). *Encephale*. 1995;21(2):107-16.
137. Endicott J, Spitzer RL, Fleiss JL, et al. The global assessment scale. A procedure for measuring overall severity of psychiatric disturbance. *Archives of General Psychiatry* 1976;33(6):766-71.

138. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry* 2008 Mar;69(3):441-51. PMID: 18294022.
139. Loo CK, Taylor JL, Gandevia SC, et al. Transcranial magnetic stimulation (TMS) in controlled treatment studies: are some "sham" forms active? *Biological Psychiatry* 2000;47(4):325-31.
140. George MS, Nahas Z, Borckardt JJ, et al. Vagus nerve stimulation for the treatment of depression and other neuropsychiatric disorders. *Expert Review of Neurotherapeutics* 2007;7(1):63-74.
141. Ware JE, Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Medical Care* 1992;30(6):473-83.
142. Kind P, ed. *The EuroQol instrument: An index of health-related quality of life. Quality of life and pharmacoeconomics in clinical trials.* 2nd ed: Philadelphia Lippincott-Raven Publishers; 1996.
143. Lisanby SH, Lubner B, Schlaepfer TE, et al. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology* 2003 Oct;28(10):1852-65. PMID: 12865903.
144. White PF, Amos Q, Zhang Y, et al. Anesthetic considerations for magnetic seizure therapy: a novel therapy for severe depression. *Anesth Analg* 2006;103(1):76-80, table of contents. PMID: 16790630.
145. Kirov G, Ebmeier KP, Scott AI, et al. Quick recovery of orientation after magnetic seizure therapy for major depressive disorder. *Br J Psychiatry* 2008 Aug;193(2):152-5. PMID: 18670002.
146. Malone DA, Jr., Dougherty DD, Rezai AR, et al. Deep brain stimulation of the ventral capsule/ventral striatum for treatment-resistant depression. *Biol Psychiatry* 2009;65(4):267-75. PMID:
147. McNeely HE, Mayberg HS, Lozano AM, et al. Neuropsychological impact of Cg25 deep brain stimulation for treatment-resistant depression: preliminary results over 12 months. *J Nerv Ment Dis* 2008 May;196(5):405-10. PMID: 18477883.
148. Mayberg HS, Lozano AM, Voon V, et al. Deep brain stimulation for treatment-resistant depression. *Neuron* 2005 Mar 3;45(5):651-60. PMID: 15748841.
149. Kenny MA, Williams JM. Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy. *Behav Res Ther* 2007 Mar;45(3):617-25. PMID: 16797486.

Appendix A. Search Strategy

TRD Search 06.23.09

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	110342
#2	Search #1 Limits: Entrez Date from 1980/01/01, Humans, English, All Adult: 19+ years	56274
#3	Search #2 Limits: Editorial, Letter, Case Reports	7200
#5	Search "Case Control Studies"[Mesh]	421177
#6	Search #2 AND #5	3156
#7	Search #3 OR #6	10272
#8	Search #2 NOT #7	46002
	Depression articles limited to English, Human, and Adults, with no editorials, letters, case reports or case-control studies.	
#9	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	123383
#10	Search #8 AND #9	2910
#11	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	379438
#12	Search #10 AND #11	48
	48 Psychotherapy/CBT/Depression articles limited to the "refractory" terms.	
#13	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	10514
#14	Search #8 AND #13	1112
#16	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	392864
	These are the terms used for RCTs.	
#17	Search #14 AND #16	203
	There are 203 RCTs about Depression and ECT.	
#18	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	1992678
#19	Search #14 AND #18	361
	There are 361 "observational studies" about Depression and ECT.	
#20	Search #17 OR #19	447
	Combining the RCTs and Observational studies for the ECT literature here.	
#21	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	2864
#22	Search #8 AND #21	141
	141 TMS articles.	
#23	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	808
#24	Search #8 AND #23	37
	37 VNS articles.	
#25	Search #12 OR #20 OR #22 OR #24	649
	Combining all results for the main search here: Psychotherapy, ECT, TMS, and VNS.	

Final number of records after duplicates removed

630

A search with analogous terms was performed in the following databases:

Embase = **269 (159 after duplicates removed)**

PsycINFO= **422 (296 after duplicates removed)**

Cochrane = 6 (no duplicates found)

EndNote file for the main search = 1346 (1074 after duplicates removed)

TRD Update Search 11.18.2010

Search	Most Recent Queries	Result
#1	Search "Depression"[Mesh] OR "Depressive Disorder"[Mesh]	120871
#2	Search ((#1) AND "2009/04/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	9152
#3	Search #2 Limits: Editorial, Letter, Case Reports	909
#4	Search "Case Control Studies"[Mesh]	476252
#5	Search #2 AND #4	558
#6	Search #3 OR #5	1460
#7	Search #2 NOT #6	7692
#8	Search "Socioenvironmental Therapy"[Mesh] OR "interpersonal psychotherapy"[tw] OR "ipt"[tw] OR "psychotherapy"[mesh] OR "Cognitive Therapy"[Mesh] OR "cognitive behavioral therapy"[tw] OR "cbt"[tw]	131504
#9	Search #7 AND #8	758
#10	Search "Drug Resistance"[Mesh] OR refractory[tw] OR resistant[tw]	414955
#11	Search #9 AND #10	25
#12	Search "Electroconvulsive Therapy"[Mesh] OR "ect"[tw] OR "electroconvulsive therapy"[tw]	11003
#13	Search #2 AND #12	149
#14	Search "Randomized Controlled Trial"[Publication Type] OR "Randomized Controlled Trials as Topic"[Mesh] OR "Single-Blind Method"[Mesh] OR "Double-Blind Method"[Mesh] OR "Random Allocation"[Mesh]	431969
#15	Search #13 AND #14	21
#16	Search "Longitudinal Studies"[Mesh] OR "Comparative Study "[Publication Type]) OR "Cohort Studies"[Mesh] OR "observational studies"[tw]	2109685
#17	Search #13 AND #16	27
#18	Search #15 OR #17	37
#19	Search "Transcranial Magnetic Stimulation"[Mesh] OR "(r)tms"[tw]	3733
#20	Search #2 AND #19	78
#21	Search "Vagus Nerve Stimulation"[Mesh] OR "vagus nerve stimulation"[tw]	988
#22	Search #2 AND #21	18
#23	Search #22 OR #20 OR #18 OR #11	143
#24	Search #23 Limits: Humans, English, All Adult: 19+ years Sort by: PublicationDate	77
#25	Search #23	143

A search with analogous terms was performed in the following databases:

PubMed 76 (77 before duplicates removed)

Embase 80 (187 before duplicates removed)

PsycINFO 170 (211 before duplicates removed)

The Cochrane Library 26 (27 before duplicates removed)

EndNote file for the Update Search = 352 (before being added to main database and duplicates removed)

TRD Pharmacologic Search (Key Question 1b)

Search	Most Recent Queries	Result
#1 Search "Antidepressive Agents"[MeSH]		37171
#2 Search "Fluoxetine"[Mesh] OR "Sertraline"[Mesh] OR "Paroxetine"[Mesh] OR "Citalopram"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "nefazodone "[Substance Name] OR "mirtazapine "[Substance Name] OR "venlafaxine "[Substance Name] OR "desmethylcitalopram "[Substance Name] OR Escitalopram[tw] OR "duloxetine "[Substance Name] OR "Trazodone"[Mesh] OR "O-desmethylvenlafaxine "[Substance Name] OR "Imipramine"[Mesh] OR "Desipramine"[Mesh] OR "Nortriptyline"[Mesh] OR "Amitriptyline"[Mesh] OR "Phenelzine"[Mesh] OR "Tranlycypromine"[Mesh] OR "Doxepin"[Mesh] OR "Clomipramine"[Mesh] OR "Maprotiline"[Mesh]		39294
#3 Search Fluoxetine OR Sertraline OR Paroxetine OR Citalopram OR Fluvoxamine OR Bupropion OR Nefazodone OR Mirtazapine OR Venlafaxine OR Escitalopram OR Duloxetine OR Trazodone OR Desvenlafaxine OR Imipramine OR Desipramine OR Nortriptyline OR Amitriptyline OR Phenelzine OR Tranlycypromine OR Doxepin OR Clomipramine OR Maprotiline		48657
#4 Search #1 OR #2 OR #3		70932
#5 Search ("Depression"[MeSH] or "Depressive Disorder"[MeSH])		113094
#6 Search "Drug Resistance"[MeSH] OR refractory[tw] OR resistant[tw]		387599
#7 Search #4 AND #5 AND #6		1359
#8 Search ("1980"[Entrez Date] : "3000"[Entrez Date]) AND (#7) Limits: Humans, English		1075
#9 Search #8 Limits: Editorial, Letter, Case Reports		222
#10 Search #8 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years		105
#11 Search #8 NOT(#9 OR #10) Sort by: Title		758
Final number of records after duplicates removed (in comparison with the main TRD nonpharmacologic database).		663

A search with analogous terms was performed in the following databases:

EMBASE (unduplicated) = 78

PsycINFO (unduplicated)= 171

Unduplicated EndNote file for the main search = 912

TRD Pharmacologic Search (KQ1b) 11.19.2010

Search	Most Recent Queries	Result
#1	Search "Antidepressive Agents"[MeSH]	39236
#2	Search "Fluoxetine"[Mesh] OR "Sertraline"[Mesh] OR "Paroxetine"[Mesh] OR "Citalopram"[Mesh] OR "Fluvoxamine"[Mesh] OR "Bupropion"[Mesh] OR "nefazodone "[Substance Name] OR "mirtazapine "[Substance Name] OR "venlafaxine "[Substance Name] OR "desmethylcitalopram "[Substance Name] OR Escitalopram[tw] OR "duloxetine "[Substance Name] OR "Trazodone"[Mesh] OR "O-desmethylvenlafaxine "[Substance Name] OR "Imipramine"[Mesh] OR "Desipramine"[Mesh] OR "Nortriptyline"[Mesh] OR "Amitriptyline"[Mesh] OR "Phenelzine"[Mesh] OR "Tranlycypromine"[Mesh] OR "Doxepin"[Mesh] OR "Clomipramine"[Mesh] OR "Maprotiline"[Mesh]	40799
#3	Search Fluoxetine OR Sertraline OR Paroxetine OR Citalopram OR Fluvoxamine OR Bupropion OR Nefazodone OR Mirtazapine OR Venlafaxine OR Escitalopram OR Duloxetine OR Trazodone OR Desvenlafaxine OR Imipramine OR Desipramine OR Nortriptyline OR Amitriptyline OR Phenelzine OR Tranlycypromine OR Doxepin OR Clomipramine OR Maprotiline	50880
#4	Search #1 OR #2 OR #3	74378
#5	Search ("Depression"[MeSH] or "Depressive Disorder"[MeSH])	120871
#6	Search "Drug Resistance"[MeSH] OR refractory[tw] OR resistant[tw]	415078
#7	Search #4 AND #5 AND #6	1465
#8	Search ((#7) AND "2009/09/01"[Entrez Date] : "3000"[Entrez Date]) AND "0"[Entrez Date] : "3000"[Entrez Date]	78
#9	Search #8 Limits: Editorial, Letter, Case Reports	8
#10	Search #8 NOT #9	70
#11	Search #10 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	7
#12	Search #10 NOT #11	63
#13	Search ("Amoxapine"[Mesh] OR "Protriptyline"[Mesh]) OR "Selegiline"[Mesh]	2578
#14	Search "Amoxapine" OR "Protriptyline" OR "Selegiline"	3228
#15	Search #13 OR #14	3228
#16	Search #15 AND #5 AND #6	16
#17	Search #16 Limits: Editorial, Letter, Case Reports	7
#18	Search #16 NOT #17	9
#19	Search #18 Limits: All Infant: birth-23 months, All Child: 0-18 years, Newborn: birth-1 month, Infant: 1-23 months, Preschool Child: 2-5 years, Child: 6-12 years, Adolescent: 13-18 years	0
#20	Search #12 OR #18	72
#21	Search #20 Limits: Humans, English	60

A search with analogous terms was performed in the following databases:

PubMed 60 (60 before duplicates removed)

Embase 131 (172 before duplicates removed)

PsycINFO 51 (69 before duplicates removed)

The Cochrane Library 66 (73 before duplicates removed)

EndNote file for the Update Search = 308 (before being added to the main EndNote Database and duplicates removed)

Appendix B. Data Abstraction Forms and Quality Rating Criteria

Inclusion/Exclusion Criteria for Abstract Review

1. Original research (no review articles, editorials, letters to the editor) published in English?

- Yes
 No
 Cannot determine

2. Study was conducted in adult patients with treatment resistant depression (two or more failed prior adequate trials of an evidence-based intervention) and compares at least one of the following interventions with another, a pharmacological intervention or placebo (check all that apply):

- A - Electroconvulsive Therapy (ECT)
 B - Repetitive Transcranial Magnetic Stimulation (rTMS)
 C - Vagus Nerve Stimulation
 D - Psychotherapy such as Cognitive Behavioral Therapy (CBT) or Interpersonal Therapy (IPT)
 E - Placebo
 F - Pharmacological intervention
 G - Deep Brain Stimulation
 H - Magnetic Seizure Therapy
 I - Other?
 J - Cannot determine
 K - None of the above (i.e. not adults, not TRD, not a relevant intervention)

3. (Only answer this if you chose K in the above question, otherwise skip #3)

Has no comparison but is in adults with TRD, examining one of the nonpharmacological interventions, for example it is a case series looking at 40 recipients of magnetic seizure therapy?

- Yes
 No

4. Addresses one or more of the following key questions (check all that apply):

- KQ1 For adults with treatment-resistant depression (TRD, defined as two or more failed adequate trials of a biologic intervention), do non-pharmacologic interventions such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), or an evidence-based psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?
- KQ2- For adults with TRD, do non-pharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?
- KQ3 Do non-pharmacologic interventions (single or combination) differ in their efficacy or

effectiveness for treating TRD as a function of particular symptom subtypes (e.g., catatonic (frozen or hyper) or psychotic symptoms)?

KQ4 For adults with treatment-resistant depression, do non-pharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to: amnesia, memory loss, headaches, post-operative complications.

KQ5 How does the efficacy, effectiveness, or harms of treatment with non-pharmacologic treatments for treatment-resistant depression differ for subpopulations?

KQ6 For adults with treatment-resistant depression, do non-pharmacologic interventions differ in regards to other health-related outcomes (e.g., quality of life)?

Cannot determine

None of the above

5. Study design is one of the following:

RCT

Systematic review (Qualitative or quantitative)

Observational Study

Other?

Cannot determine

Case series (no comparison arm)

6. Use for background ? (If Yes, check and flag article)

Yes

No

Inclusion/Exclusion Criteria for Full Text Review

1. Should the article be excluded for any of the following reasons?

Study reported only in abstract (Full text is not available)

Background article

Wrong outcome (i.e. not validated tool, pharmacokinetic or other intermediate outcomes)

Wrong intervention

No relevant comparison and no report of adverse events, harms or adherence

No relevant comparison BUT reports of adverse events, harms or adherence

Wrong population (For example no pediatric or perinatal studies or patients not TRD or analysis does not break out patients with TRD)

Wrong publication type (e.g. letter or editorial)

Other? (Please explain!)

None of the above- should be included!

2. Addresses one or more of the following key questions (check all that apply):

KQ1 For adults with depression, do non-pharmacologic interventions such as electroconvulsive therapy (ECT), vagus nerve stimulation (VNS), repetitive transcranial magnetic stimulation (TMS), or an evidence-based psychotherapy (e.g., cognitive therapy [CBT or IPT]) differ in efficacy or effectiveness in treating acute phase depressive symptoms (e.g., response and remission), whether as a single treatment or part of a combination treatment?

KQ2- For adults with depression, do non-pharmacologic interventions differ in their efficacy or effectiveness for maintaining response or remission (e.g., preventing relapse or recurrence) whether as a single treatment or part of a combination treatment?

KQ3 Do non-pharmacologic interventions (single or combination) differ in their efficacy or effectiveness for treating depression as a function of particular symptom subtypes (e.g., catatonic (frozen or hyper) or psychotic symptoms)?

KQ4 For adults with depression, do non-pharmacologic interventions differ in safety, adverse events, or adherence? Adverse effects of interest include but are not limited to: amnesia, memory loss, headaches, post-operative complications.

KQ5 How do the efficacy, effectiveness, or harms of treatment with non-pharmacologic treatments for depression differ for subpopulations?

KQ6 For adults with depression, do non-pharmacologic interventions differ in regards to other health-related outcomes (e.g., quality of life)?

Cannot determine

None of the above

3. Study population has previously been treated

Two or more treatments for depression

One or more treatments for depression

No previous treatments for depression

Not reported but referred to as TRD or refractory

Other? (Please explain)

4. Study design is one of the following:

RCT

Systematic review (Qualitative or quantitative)

- Observational Study
- Other?
- Cannot determine
- Case series (no comparison arm)

Internal Validity Quality Forms

Quality for Experimental Studies

1. Randomization adequate?

- Yes
- No
- Not randomized
- Method not reported

2. Allocation concealment adequate?

- Yes
- No
- Not randomized
- Method not reported

3. Was the sample size sufficient to detect appropriate changes in the outcomes of interest? (i.e. was there an explanation of the statistical power?)

- Yes
- No

4. Groups similar at baseline?

- Yes
- No

5. Outcome assessors masked?

- Yes
- No
- Yes, but method not described
- Not reported

6. Care provider masked?

- Yes
- No
- Yes, but method not described

- Not reported
7. Patient masked?
- Yes
- No
- Yes, but method not described
- Not reported
8. Overall attrition high ($\geq 20\%$)?
- Yes (please state how high)
- No
9. Differential attrition high ($\geq 15\%$)?
- Yes (please state difference)
- No
10. Was the statistical analysis based on intention-to-treat (ITT)?
- Yes
- No
- Cannot tell
11. Were outcome measures valid, reliable, and equally applied?
- Yes
- No
12. Were there any post-randomization exclusions?
- Yes (how many?)
- No
- Cannot tell
13. Methods of adverse effects assessment
- Patient reported
- Physical exam at study visits
- Lab evaluations
- Standardized scale (e.g. WHO, UKU-SES)
- other (please specify)
- Not applicable
14. Adverse events pre-specified and defined?
- Yes

No

Not applicable

15. Ascertainment techniques for detecting adverse events non-biased and adequately described?

Yes

No

Not applicable

16. Quality rating for experimental study (RCT)

Good

Fair

Poor

If poor, why?

Quality Review for Observational Studies

1. Were both groups selected from the same source population?

Yes

No

Yes, but method not described

Not reported

2. Did both groups have the same risk of having the outcome of interest at baseline?

Yes

No

Not reported

Not applicable

3. Were subjects in both groups recruited over the same time period?

Yes

No

Yes, but method not described

Not reported

Not applicable

4. Were measurement methods adequate and equally applied to both groups?

Yes

No

Not reported

Not applicable

5. Does the analysis control for baseline differences?

Yes

No

Not applicable

6. Were important potential confounding and modifying variables taken into account in the design and analysis (i.e. through matching, stratification, or statistical adjustment)?

Yes

No

Not applicable

7. Were the statistical methods used to assess the abstracted outcomes appropriate?

Yes

No

Not applicable

8. Was the sample size sufficient to detect appropriate changes in the outcomes of interest? (i.e. was there an explanation of the statistical power?)

Yes

No

9. Was an attempt made to blind the outcome assessors?

Yes

No

Yes, but method not described

Not reported

Not applicable

10. Was the time of follow-up equal in both groups?

Yes

No

Not reported

Not applicable

11. Overall attrition high ($\geq 20\%$)?

Yes (please state how high)

No

12. Differential attrition high ($\geq 15\%$)?

Yes (please state difference)

No

Not applicable

13. Methods of adverse effects assessment

Patient reported

Physical exam at study visits

Lab evaluations

Standardized scale (e.g. WHO, UKU-SES)

other (please specify)

Not applicable

14. Adverse events pre-specified and defined?

Yes

No

Not applicable

15. Ascertainment techniques for detecting adverse events non-biased and adequately described?

Yes

No

Not applicable

16. Quality rating for observational study?

Good

Fair

Poor - why?

Appendix C. Excluded Studies

No or Wrong Comparison

1. Abbass AA. Intensive short-term dynamic psychotherapy of treatment-resistant depression: a pilot study. *Depress Anxiety*. 2006;23(7):449-52.
2. Abraham G, Milev R, Lazowski L, Jokic R, du Toit R, Lowe A. Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression--An open label trial. *Neuropsychiatric Disease and Treatment*. 2007 2007;3(6):919-24.
3. Abrams R, Swartz CM, Vedak C. Antidepressant effects of high-dose right unilateral electroconvulsive therapy. *Arch Gen Psychiatry*. 1991 Aug;48(8):746-8.
4. Achiffier F, Stinchfield Z, Pascual-Leone A. Prediction of clinical response to transcranial magnetic stimulation for depression by baseline lateral visual-field stimulation. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*. 2002 Mar 2002;15(1):18-27.
5. Antonuccio DO, Akins WT, Chatham PM, Monagin JA, Tearnan BH, Ziegler BL. An exploratory study: the psychoeducational group treatment of drug-refractory unipolar depression. *J Behav Ther Exp Psychiatry*. 1984 Dec;15(4):309-13.
6. Aoyama Y, Hanaoka N, Kameyama M, Suda M, Sato T, Song M, et al. Stimulus intensity dependence of cerebral blood volume changes in left frontal lobe by low-frequency rTMS to right frontal lobe: A near-infrared spectroscopy study. *Neurosci Res*. 2009 Jan;63(1):47-51.
7. Aronson TA, Shukla S, Hoff A, Cook B. Proposed delusional depression subtypes: preliminary evidence from a retrospective study of phenomenology and treatment course. *J Affect Disord*. 1988 Jan-Feb;14(1):69-74.
8. Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008 Mar;69(3):441-51.
9. Avramov MN, Stool LA, White PF, Husain MM. Effects of nicardipine and labetalol on the acute hemodynamic response to electroconvulsive therapy. *Journal of Clinical Anesthesia*. 1998;10(5):394-400.
10. Bailine SH, Rifkin A, Kayne E, Selzer JA, Vital-Herne J, Blika M, et al. Comparison of bifrontal and bitemporal ECT for major depression. *Am J Psychiatry*. 2000 Jan;157(1):121-3.
11. Bajbouj M, Gallinat J, Lang UE, Hellen F, Vesper J, Lisanby SH, et al. Motor cortex excitability after vagus nerve stimulation in major depression. *J Clin Psychopharmacol*. 2007 Apr;27(2):156-9.
12. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. *Journal of Clinical Psychiatry*. 2002;63(8):737-41.
13. Bauer M, Pfennig A, Linden M, Smolka MN, Neu P, Adli M. Efficacy of an algorithm-guided treatment compared with treatment as usual: a randomized, controlled study of inpatients with depression. *J Clin Psychopharmacol*. 2009 Aug;29(4):327-33.
14. Beale MD, Kellner CH, Pritchett JT, Bernstein HJ, Burns CM, Knapp R. Stimulus dose-titration in ECT: A 2-year clinical experience. *Convulsive Therapy*. 1994;10(2):171-6.
15. Bean GJ, Marchese V, Martin BA. Electric stimulus energy and the clinical response to electroconvulsive therapy. *Can J Psychiatry*. 1991 Nov;36(9):637-44.
16. Beasley CM, Jr., Sayler ME, Cunningham GE, Weiss AM, Masica DN. Fluoxetine in tricyclic refractory major depressive disorder. *J Affect Disord*. 1990 Nov;20(3):193-200.

17. Bergsholm P, Larsen JL, Rosendahl K, Holsten F. Electroconvulsive therapy and cerebral computed tomography. A prospective study. *Acta Psychiatr Scand*. 1989 Dec;80(6):566-72.
18. Beutler LE, Engle D, Mohr D, Daldrup RJ, Bergan J, Meredith K, et al. Predictors of differential response to cognitive, experiential, and self-directed psychotherapeutic procedures. *J Consult Clin Psychol*. 1991 Apr;59(2):333-40.
19. Birkenhager TK, Renes JW, Pluijms EM. One-year follow-up after successful ECT: a naturalistic study in depressed inpatients. *J Clin Psychiatry*. 2004 Jan;65(1):87-91.
20. Birkenhager TK, van den Broek WW, Moleman P, Bruijn JA. Outcome of a 4-step treatment algorithm for depressed inpatients. *J Clin Psychiatry*. 2006 Aug;67(8):1266-71.
21. Birkenhager TK, Van Den Broek WW, Mulder PGH, De Lely A. One-year outcome of psychotic depression after successful electroconvulsive therapy. *J ECT*. 2005;21(4):221-6.
22. Birkenhäger TK, van den Broek WW, Wijkstra J, Bruijn JA, van Os E, Boks M, et al. Treatment of unipolar psychotic depression: An open study of lithium addition in refractory psychotic depression. *Journal of Clinical Psychopharmacology*. 2009;29(5):513-5.
23. Bosboom PR, Deijen JB. Age-related cognitive effects of ECT and ECT-induced mood improvement in depressive patients. *Depress Anxiety*. 2006;23(2):93-101.
24. Bowman ES, Coons PM. The use of electroconvulsive therapy in patients with dissociative disorders. *Journal of Nervous and Mental Disease*. 1992 Aug 1992;180(8):524-8.
25. Brodaty H, Berle D, Hickie I, Mason C. "Side effects" of ECT are mainly depressive phenomena and are independent of age. *J Affect Disord*. 2001 Oct;66(2-3):237-45.
26. Brodaty H, Hickie I, Mason C, Prenter L. A prospective follow-up study of ECT outcome in older depressed patients. *J Affect Disord*. 2000 Nov;60(2):101-11.
27. Bulbena A, Berrios GE. Cognitive function in the affective disorders: a prospective study. *Psychopathology*. 1993;26(1):6-12.
28. Butterfield NN, Graf P, Macleod BA, Ries CR, Zis AP. Propofol reduces cognitive impairment after electroconvulsive therapy. *J Ect*. 2004 Mar;20(1):3-9.
29. Calev A, Nigal D, Shapira B, Tubi N, Chazan S, Ben-Yehuda Y, et al. Early and long-term effects of electroconvulsive therapy and depression on memory and other cognitive functions. *J Nerv Ment Dis*. 1991 Sep;179(9):526-33.
30. Carty JA. An examination of the relative effectiveness of three cognitive behavioral group treatments for depression in an Australian treatment-resistant population. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2001 Jul 2001;62(1):539.
31. Casey P, Meagher D, Butler E. Personality, functioning, and recovery from major depression. *J Nerv Ment Dis*. 1996 Apr;184(4):240-5.
32. Catafau AM, Perez V, Gironell A, Martin JC, Kulisevsky J, Estorch M, et al. SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients: A pilot study. *Psychiatry Res: Neuroimaging*. 2001 May 2001;106(3):151-60.
33. Clark CP, Alexopoulos GS, Kaplan J. Prolactin release and clinical response to electroconvulsive therapy in depressed geriatric inpatients: a preliminary report. *Convuls Ther*. 1995 Mar;11(1):24-31.
34. Cohen Y, Feldinger E, Ogorek D, Weinbroum AA. Increased propofol requirement during succeeding administrations for electroconvulsive therapy. *J Clin Anesth*. 2004 Jun;16(4):282-5.
35. Coleman EA, Sackeim HA, Prudic J, Devanand DP, McElhiney MC, Moody BJ. Subjective memory complaints prior to and following electroconvulsive therapy. *Biol Psychiatry*. 1996 Mar 1;39(5):346-56.
36. Coppen A, Abou-Saleh MT, Milln P, Bailey J, Metcalfe M, Burns BH, et al. Lithium continuation therapy following electroconvulsive therapy. *Br J Psychiatry*. 1981 Oct;139:284-7.

37. Corcoran CD, Thomas P, Phillips J, O'Keane V. Vagus nerve stimulation in chronic treatment-resistant depression: preliminary findings of an open-label study. *Br J Psychiatry*. 2006 Sep;189:282-3.
38. Criado JM, Fernandez A, Ortiz T. Long-term effects of electroconvulsive therapy on episodic memory. *Actas Esp Psiquiatr*. 2007 Jan-Feb;35(1):40-6.
39. Cronholm B, Ottosson JO. Experimental studies of the therapeutic action of electroconvulsive therapy in endogenous depression. The role of the electrical stimulation and of the seizure studied by variation of stimulus intensity and modification by lidocaine of seizure discharge. *Convuls Ther*. 1996 Sep;12(3):172-94.
40. Curran S. Effect of paroxetine on seizure length during electroconvulsive therapy. *Acta Psychiatr Scand*. 1995 Sep;92(3):239-40.
41. Currier MB, Murray GB, Welch CC. Electroconvulsive therapy for post-stroke depressed geriatric patients. *J Neuropsychiatry Clin Neurosci*. 1992 Spring;4(2):140-4.
42. Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. ECT in bipolar and unipolar depression: Differences in speed of response. *Bipolar Disorders* 2001;3(2):95-104.
43. Dannon PN, Grunhaus L. Effect of electroconvulsive therapy in repetitive transcranial magnetic stimulation non-responder MDD patients: A preliminary study. *International Journal of Neuropsychopharmacology*. 2001 Sep 2001;4(3):265-8.
44. Dell'Osso B, Mundo E, D'Urso N, Pozzoli S, Buoli M, Ciabatti MT, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disorders*. 2009 Feb 2009;11(1):76-81.
45. Delva NJ, Brunet DG, Hawken ER, Kesteven RM, Lawson JS, Lywood DW, et al. Characteristics of responders and nonresponders to brief-pulse right unilateral ECT in a controlled clinical trial. *J Ect*. 2001 Jun;17(2):118-23.
46. Devanand DP, Fitzsimons L, Prudic J, Sackeim HA. Subjective side effects during electroconvulsive therapy. *Convuls Ther*. 1995 Dec;11(4):232-40.
47. Dombrowski AY, Mulsant BH, Haskett RF, Prudic J, Begley AE, Sackeim HA. Predictors of remission after electroconvulsive therapy in unipolar major depression. *J Clin Psychiatry*. 2005 Aug;66(8):1043-9.
48. Dubovsky SL, Buzan R, Thomas M, Kassner C, Cullum CM. Nicardipine improves the antidepressant action of ECT but does not improve cognition. *J Ect*. 2001 Mar;17(1):3-10.
49. Engelhardt W, Carl G, Hartung E. Intra-individual open comparison of burst-suppression-isoflurane-anaesthesia versus electroconvulsive therapy in the treatment of severe depression. *Eur J Anaesthesiol*. 1993 Mar;10(2):113-8.
50. Epstein CM, Evatt ML, Funk A, Girard-Siqueira L, Lupei N, Slaughter L, et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. *Clin Neurophysiol*. 2007 Oct;118(10):2189-94.
51. Epstein CM, Figiel GS, McDonald WM, Amazon-Leece J, Figiel L. Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. *Psychiatric Annals*. 1998 Jan 1998;28(1):36-9.
52. Eschweiler GW, Plewnia C, Batra A, Bartels M. Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*. 2000 Nov 2000;45(9):845-6.
53. Eschweiler GW, Vonthein R, Bode R, Huell M, Conca A, Peters O, et al. Clinical efficacy and cognitive side effects of bifrontal versus right unilateral electroconvulsive therapy (ECT): a short-term randomised controlled trial in pharmaco-resistant major depression. *J Affect Disord*. 2007 Aug;101(1-3):149-57.

54. Ezzat DH, Ibraheem MM, Makhawy B. The effect of Piracetam on ECT--induced memory disturbances. *Br J Psychiatry*. 1985 Dec;147:720-1.
55. Fabre I, Galinowski A, Oppenheim C, Gallarda T, Meder JF, de Montigny C, et al. Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: An open trial. *International Journal of Geriatric Psychiatry*. 2004;19(9):833-42.
56. Fava GA, Savron G, Grandi S, Rafanelli C. Cognitive-behavioral management of drug-resistant major depressive disorder. *J Clin Psychiatry*. 1997 Jun;58(6):278-82; quiz 83-4.
57. Fekadu A, Wooderson SC, Markopoulou K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J Affect Disord*. 2009 Jul;116(1-2):4-11.
58. Fenton L, Fasula M, Ostroff R, Sanacora G. Can cognitive behavioral therapy reduce relapse rates of depression after ECT? a preliminary study. *J Ect*. 2006 Sep;22(3):196-8.
59. Figiel GS, DeLeo B, Zorumski CF, Baker K, Goewert A, Jarvis M, et al. Combined use of labetalol and nifedipine in controlling the cardiovascular response from ECT. *J Geriatr Psychiatry Neurol*. 1993 Jan-Mar;6(1):20-4.
60. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry & Clinical Neurosciences*. 1998 Win 1998;10(1):20-5.
61. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J. Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. *Australian and New Zealand Journal of Psychiatry*. 2006 Sep 2006;40(9):764-8.
62. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the anti-depressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depression and Anxiety*. 2009 Mar 2009;26(3):229-34.
63. Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*. 2008 Feb;28(1):52-8.
64. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):655-66.
65. Fitzgerald PB, Sritharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *J Clin Psychopharmacol*. 2007 Oct;27(5):488-92.
66. Flint AJ, Rifat SL. Anxious depression in elderly patients. Response to antidepressant treatment. *Am J Geriatr Psychiatry*. 1997 Spring;5(2):107-15.
67. Frank E, Grochocinski VJ, Spanier CA, Buysse DJ, Cherry CR, Houck PR, et al. Interpersonal psychotherapy and antidepressant medication: Evaluation of a sequential treatment strategy in women with recurrent major depression. *Journal of Clinical Psychiatry*. 2000 Jan 2000;61(1):51-7.
68. Frasca TA, Iodice A, McCall WV. The relationship between changes in learning and memory after right unilateral electroconvulsive therapy. *J Ect*. 2003 Sep;19(3):148-50.
69. Fraser RM, Glass IB. Unilateral and bilateral ECT in elderly patients. A comparative study. *Acta Psychiatr Scand*. 1980 Jul;62(1):13-31.
70. Frederiksen SO, d'Elia G, Holsten F. Influence of ACTH 4-10 and unilateral ECT on primary and secondary memory in depressive patients. *Eur Arch Psychiatry Neurol Sci*. 1985;234(5):291-4.
71. Fu W, Stool LA, White PF, Husain MM. Acute hemodynamic responses to electroconvulsive therapy are not related to the duration of seizure activity. *Journal of Clinical Anesthesia* 1997;9(8):653-7.

72. Fu W, Stool LA, White PF, Husain MM. Is oral clonidine effective in modifying the acute hemodynamic response during electroconvulsive therapy? *Anesth Analg*. 1998;86(5):1127-30.
73. Fujita A, Nakaaki S, Segawa K, Azuma H, Sato K, Arahata K, et al. Memory, attention, and executive functions before and after sine and pulse wave electroconvulsive therapies for treatment-resistant major depression. *J Ect*. 2006 Jun;22(2):107-12.
74. Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Praveen J, Reddy AK. Twice versus thrice weekly ECT in melancholia: a double-blind prospective comparison. *J Affect Disord*. 1993 Apr;27(4):273-8.
75. Geller V, Grisaru N, Abarbanel JM, Lemberg T, Belmaker RH. Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 1997 Jan 1997;21(1):105-10.
76. George MS, Wassermann EM, Williams WA, Callahan A, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience*. 1995 Oct 1995;6(14):1853-6.
77. Gormly N, Cullen C, Watters L, Philpot M, Lawlor BA. Does psychosis predict response to ECT in depressed elderly patients? *Irish Journal of Psychological Medicine*. 1999 Mar 1999;16(1):13-5.
78. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: a controlled study. *Am J Psychiatry*. 1998 Nov;155(11):1608-10.
79. Grunhaus L, Schreiber S, Dolberg OT, Hirshman S, Dannon PN. Response to ECT in major depression: are there differences between unipolar and bipolar depression? *Bipolar Disord*. 2002;4 Suppl 1:91-3.
80. Hamilton M. The effect of treatment on the melancholias (depressions). *Br J Psychiatry*. 1982 Mar;140:223-30.
81. Healey WV, Khan A, Noonan C. Major depression with psychosis: demographic, phenomenological, and outcome characteristics in one hospitalized population. *J Nerv Ment Dis*. 1990 Nov;178(11):722-3.
82. Heikman P, Kalska H, Katila H, Sarna S, Tuunainen A, Kuoppasalmi K. Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: a preliminary study. *J Ect*. 2002 Mar;18(1):26-30.
83. Heikman P, Katila H, Sarna S, Wahlbeck K, Kuoppasalmi K. Differential response to right unilateral ECT in depressed patients: impact of comorbidity and severity of illness [ISRCTN39974945]. *BMC Psychiatry*. 2002;2:2.
84. Heikman P, Tuunainen A, Kuoppasalmi K. Value of the initial stimulus dose in right unilateral and bifrontal electroconvulsive therapy. *Psychol Med*. 1999 Nov;29(6):1417-23.
85. Hickie I, Mason C, Parker G. Comparative validity of two measures of psychomotor function in patients with severe depression. *J Affect Disord*. 1996 Apr 12;37(2-3):143-9.
86. Hickie I, Mason C, Parker G, Brodaty H. Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. *Br J Psychiatry*. 1996 Jul;169(1):68-74.
87. Horne RL, Pettinati HM, Sugerman AA, Varga E. Comparing bilateral to unilateral electroconvulsive therapy in a randomized study with EEG monitoring. *Arch Gen Psychiatry*. 1985 Nov;42(11):1087-92.
88. Huang CC, Su TP, Wei IH. Repetitive transcranial magnetic stimulation for treating medication-resistant depression in Taiwan: a preliminary study. *J Chin Med Assoc*. 2005 May;68(5):210-5.
89. Huang CC, Wei IH, Chou YH, Su TP. Effect of age, gender, menopausal status, and ovarian hormonal level on rTMS in treatment-resistant depression. *Psychoneuroendocrinology*. 2008 Jul;33(6):821-31.

90. Husain MM, McClintock SM, Rush AJ, Knapp RG, Fink M, Rummans TA, et al. The efficacy of acute electroconvulsive therapy in atypical depression. *J Clin Psychiatry*. 2008 Mar;69(3):406-11.
91. Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *J Clin Psychiatry*. 2004 Apr;65(4):485-91.
92. Husain SS, Kevan IM, Linnell R, Scott AI. Electroconvulsive therapy in depressive illness that has not responded to drug treatment. *J Affect Disord*. 2004 Dec;83(2-3):121-6.
93. Huuhka M, Korpisammal L, Haataja R, Leinonen E. One-year outcome of elderly inpatients with major depressive disorder treated with ECT and antidepressants. *J Ect*. 2004 Sep;20(3):179-85.
94. Huuhka MJ, Haanpaa ML, Leinonen EV. Electroconvulsive therapy in patients with depression and fibromyalgia. *Eur J Pain*. 2004 Aug;8(4):371-6.
95. Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, et al. Low Frequency rTMS Stimulation of the Right Frontal Cortex Is as Effective as High Frequency rTMS Stimulation of the Left Frontal Cortex for Antidepressant-Free, Treatment-Resistant Depressed Patients. *Annals of Clinical Psychiatry*. 2005 Jul-Sep 2005;17(3):153-9.
96. Jagadeesh HN, Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Jain S. Time dependent therapeutic effects of single electroconvulsive therapy (ECT) in endogenous depression. *J Affect Disord*. 1992 Apr;24(4):291-5.
97. Janakiramaiah N, Motreja S, Gangadhar BN, Subbakrishna DK, Parameshwara G. Once vs. three times weekly ECT in melancholia: A randomized controlled trial. *Acta Psychiatrica Scandinavica*. 1998;98(4):316-20.
98. Janicak PG, Sharma RP, Israni TH, Dowd SM, Altman E, Davis JM. Effects of unilateral-nondominant vs. bilateral ECT on memory and depression: a preliminary report. *Psychopharmacol Bull*. 1991;27(3):353-7.
99. Januel D, Dumortier G, Verdon CM, Stamatiadis L, Saba G, Cabaret W, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Prog Neuropsychopharmacol Biol Psychiatry*. 2006 Jan;30(1):126-30.
100. Jha A, Stein G. Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatr Scand*. 1996 Aug;94(2):101-4.
101. Johanson A, Gustafson L, Risberg J, Rosen I, Sjobeck M, Silfverskiold P. Long-term follow-up in depressed patients treated with electroconvulsive therapy. *J Ect*. 2005 Dec;21(4):214-20.
102. Katona CL. Puerperal mental illness: comparisons with non-puerperal controls. *Br J Psychiatry*. 1982 Nov;141:447-52.
103. Katsikitis M, Pridmore S, Marzullo M. The facial expression measurement system in the assessment of the efficacy of transcranial magnetic stimulation in the treatment of depression. *European Review of Applied Psychology*. 1999 1999;49(2):123-9.
104. Keller MB, Lavori PW, Rice J. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: A prospective follow-up. *Am J Psychiatry*. 1992;143:24-8.
105. Keller MB, Shapiro RW. Major depressive disorder. Initial results from a one-year prospective naturalistic follow-up study. *J Nerv Ment Dis*. 1981 Dec;169(12):761-8.
106. Kenny MA, Williams JMG. Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy. *Behaviour Research and Therapy*. 2007 Mar 2007;45(3):617-25.

107. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry*. 1999 Dec 15;46(12):1603-13.
108. Kito S, Fujita K, Koga Y. Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. *J Neuropsychiatry Clin Neurosci*. 2008 Winter;20(1):74-80.
109. Klausner EJ, Clarkin JF, Spielman L, Pupo C, Abrams R, Alexopoulos GS. Late-life depression and functional disability: the role of goal-focused group psychotherapy. *International Journal of Geriatric Psychiatry*. 1998;13(10):707-16.
110. Kok RM, Nolen WA, Heeren TJ. Outcome of late-life depression after 3 years of sequential treatment. *Acta Psychiatrica Scandinavica*. 2009;119(4):274-81.
111. Kotresh S, Girish K, Janakiramaiah N, Rao GU, Gangadhar BN. Effect of ECT stimulus parameters on seizure physiology and outcome. *J Ect*. 2004 Mar;20(1):10-2.
112. Krystal AD, Holsinger T, Weiner RD, Coffey CE. Prediction of the utility of a switch from unilateral to bilateral ECT in the elderly using treatment 2 ictal EEG indices. *J Ect*. 2000 Dec;16(4):327-37.
113. Lang UE, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology (Berl)*. 2006 Jul;187(1):56-9.
114. Langer G, Karazman R, Neumark J, Saletu B, Schonbeck G, Grunberger J, et al. Isoflurane наркоtherapy in depressive patients refractory to conventional antidepressant drug treatment. A double-blind comparison with electroconvulsive treatment. *Neuropsychobiology*. 1995;31(4):182-94.
115. Lehmann HE, Fenton FR, Deutsch M, Feldman S, Engelsmann F. An 11-year follow-up study of 110 depressed patients. *Acta Psychiatr Scand*. 1988 Jul;78(1):57-65.
116. Lekwauwa R, McQuoid D, Steffens DC. Hippocampal volume is associated with physician-reported acute cognitive deficits after electroconvulsive therapy. *J Geriatr Psychiatry Neurol*. 2006 Mar;19(1):21-5.
117. Lerer B, Shapira B, Calev A, Tubi N, Drexler H, Kindler S, et al. Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. *Am J Psychiatry*. 1995 Apr;152(4):564-70.
118. Letemendia FJ, Delva NJ, Rodenburg M, Lawson JS, Inglis J, Waldron JJ, et al. Therapeutic advantage of bifrontal electrode placement in ECT. *Psychol Med*. 1993 May;23(2):349-60.
119. Leung M, Hollander Y, Brown GR. Pretreatment with ibuprofen to prevent electroconvulsive therapy-induced headache. *J Clin Psychiatry*. 2003 May;64(5):551-3.
120. Levine J, Swartz M, Feibel H, Schreiber G. Premedication with non-selective and M1-selective muscarinic antagonists before ECT. *Isr J Psychiatry Relat Sci*. 1993;30(3):179-82.
121. Levitt AJ, Joffe RT, Kamil R, McIntyre R. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J Clin Psychiatry*. 1999 Sep;60(9):613-6.
122. Li X, Nahas Z, Lomarev M, Denslow S, Shastri A, Bohning DE, et al. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: a magnetic resonance imaging study in patients with depression. *Cogn Behav Neurol*. 2003 Jun;16(2):128-35.
123. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology*. 2003 Oct;28(10):1852-65.
124. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry*. 2000 Jun;57(6):581-90.

125. Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol.* 2000 Apr;13(2):119-24.
126. Locala JA, Irefin SA, Malone D, Cywinski JB, Samuel SW, Naugle R. The comparative hemodynamic effects of methohexital and remifentanyl in electroconvulsive therapy. *J Ect.* 2005 Mar;21(1):12-5.
127. Luborzewski A, Schubert F, Seifert F, Danker-Hopfe H, Brakemeier EL, Schlattmann P, et al. Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *J Psychiatr Res.* 2007 Oct;41(7):606-15.
128. Lykouras E, Malliaras D, Christodoulou GN, Papakostas Y, Voulgari A, Tzonou A, et al. Delusional depression: phenomenology and response to treatment. A prospective study. *Acta Psychiatr Scand.* 1986 Mar;73(3):324-9.
129. Magni G, Fisman M, Helmes E. Clinical correlates of ECT-resistant depression in the elderly. *J Clin Psychiatry.* 1988 Oct;49(10):405-7.
130. Malaspina D, Amador XF, Coleman EA, Mayr TL, Friedman JH, Sackeim HA. Smooth pursuit eye movement abnormality in severe major depression: effects of ECT and clinical recovery. *J Neuropsychiatry Clin Neurosci.* 1994 Winter;6(1):36-42.
131. Malitz S, Sackeim H, Decina P. Low dosage ECT: Electrode placement and acute physiological and cognitive effects. *Am J Psychiatry.* 1984;4:47-53.
132. Malitz S, Sackeim HA, Decina P, Kanzler M, Kerr B. The efficacy of electroconvulsive therapy. Dose-response interactions with modality. *Ann N Y Acad Sci.* 1986;462:56-64.
133. Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry.* 2002 Feb 15;51(4):280-7.
134. Martis B, Alam D, Dowd SM, Hill SK, Sharma RP, Rosen C, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin Neurophysiol.* 2003 Jun;114(6):1125-32.
135. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron.* 2005 Mar 3;45(5):651-60.
136. Mayur PM, Shree RS, Gangadhar BN, Subbakrishna DK, Janakiramaiah N, Rao GSU. Atropine premedication and the cardiovascular response to electroconvulsive therapy. *British Journal of Anaesthesia.* 1998;81(3):466-7.
137. McCall WV, Colenda CC, Farah BA. Ictal EEG regularity declines during a course of RUL ECT. *Convuls Ther.* 1996 Dec;12(4):213-6.
138. McCall WV, Dunn A, Rosenquist PB. Quality of life and function after electroconvulsive therapy. *Br J Psychiatry.* 2004 Nov;185:405-9.
139. McCall WV, Dunn A, Rosenquist PB, Hughes D. Markedly suprathreshold right unilateral ECT versus minimally suprathreshold bilateral ECT: antidepressant and memory effects. *J Ect.* 2002 Sep;18(3):126-9.
140. McCall WV, Farah BA, Reboussin D, Colenda CC. Comparison of the efficacy of titrated, moderate-dose and fixed, high-dose right unilateral ECT in elderly patients. *American Journal of Geriatric Psychiatry.* 1995;3(4):317-24.
141. McCall WV, Reboussin BA, Cohen W, Lawton P. Electroconvulsive therapy is associated with superior symptomatic and functional change in depressed patients after psychiatric hospitalization. *J Affect Disord.* 2001 Mar;63(1-3):17-25.
142. McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry.* 2000 May;57(5):438-44.

143. McDonald WM, Easley K, Byrd EH, Holtzheimer P, Tuohy S, Woodard JL, et al. Combination rapid transcranial magnetic stimulation in treatment refractory depression. *Neuropsychiatric Disease and Treatment*. 2006 Jan 2006;2(1):85-94.
144. McPherson S, Cairns P, Carlyle J, Shapiro DA, Richardson P, Taylor D. The effectiveness of psychological treatments for treatment-resistant depression: a systematic review. *Acta Psychiatr Scand*. 2005 May;111(5):331-40.
145. Meyers BS, Klimstra SA, Gabriele M, Hamilton M, Kakuma T, Tirumalasetti F, et al. Continuation treatment of delusional depression in older adults. *Am J Geriatr Psychiatry*. 2001 Fall;9(4):415-22.
146. Meyers BS, Mei-Tal V. Empirical study on an inpatient psychogeriatric unit: biological treatment in patients with depressive illness. *Int J Psychiatry Med*. 1985;15(2):111-24.
147. Miller IW, Bishop SB, Norman WH, Keitner GI. Cognitive/behavioural therapy and pharmacotherapy with chronic, drug-refractory depressed inpatients: A note of optimism. *Behavioural Psychotherapy*. 1985 Oct 1985;13(4):320-7.
148. Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, et al. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clin Neurophysiol*. 2005 May;116(5):1062-71.
149. Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B, Johnson KA, et al. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. *Biol Psychiatry*. 2004 Apr 15;55(8):816-25.
150. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*. 1999 Jul;156(7):1000-6.
151. Mulsant BH, Rosen J, Thornton JE, Zubenko GS. A prospective naturalistic study of electroconvulsive therapy in late-life depression. *J Geriatr Psychiatry Neurol*. 1991 Jan-Mar;4(1):3-13.
152. Nahas Z, Kunik ME, Orengo CA, Molinari V, Workman R. Depression in male geropsychiatric inpatients with and without dementia: a naturalistic study. *J Affect Disord*. 1997 Dec;46(3):243-6.
153. Nahas Z, Li X, Kozel FA, Mirzki D, Memon M, Miller K, et al. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. *Depress Anxiety*. 2004;19(4):249-56.
154. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005 Sep;66(9):1097-104.
155. Nakajima S, Ishida T, Akaishi R, Takahata K, Kitahata R, Uchida H, et al. Impacts of switching antidepressants after successful electroconvulsive therapy on the maintenance of clinical remission in patients with treatment-resistant depression: A chart review. *The Journal of ECT*. 2009;25(3):178-81.
156. Navarro V, Gasto C, Lomena F, Mateos JJ, Portella MJ, Massana G, et al. Frontal cerebral perfusion after antidepressant drug treatment versus ECT in elderly patients with major depression: a 12-month follow-up control study. *J Clin Psychiatry*. 2004 May;65(5):656-61.
157. Neu P, Heuser I, Bajbouj M. Cerebral blood flow during vagus nerve stimulation--a transcranial Doppler study. *Neuropsychobiology*. 2005;51(4):265-8.
158. Ng RMK. Cognitive Therapy for Obsessive-compulsive Personality Disorder - A Pilot Study in Hong Kong Chinese Patients. *Hong Kong J Psychiatry*. 2005 Jun 2005;15(2):50-3.
159. Nguyen TT, Chhibber AK, Lustik SJ, Kolano JW, Dillon PJ, Guttmacher LB. Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy. *British Journal of Anaesthesia*. 1997;79(6):801-3.

160. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, et al. Decreased regional brain metabolism after ect. *Am J Psychiatry*. 2001 Feb;158(2):305-8.
161. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, et al. Treatment strategy in depression. II. MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatr Scand*. 1988 Dec;78(6):676-83.
162. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry*. 2001 Fall;9(4):382-90.
163. O'Keane V, Dinan TG, Scott L, Corcoran C. Changes in hypothalamic-pituitary-adrenal axis measures after vagus nerve stimulation therapy in chronic depression. *Biol Psychiatry*. 2005 Dec 15;58(12):963-8.
164. O'Leary D, Gill D, Gregory S, Shawcross C. Which depressed patients respond to ECT? The Nottingham results. *Journal of Affective Disorders* 1995;33(4):245-50.
165. O'Leary DA, Lee AS. Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. *Br J Psychiatry*. 1996 Oct;169(4):423-9.
166. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J Ect*. 2004 Mar;20(1):13-20.
167. Parker G, Hadzi-Pavlovic D, Hickie I, Mitchell P, Wilhelm K, Brodaty H, et al. Psychotic depression: a review and clinical experience. *Aust N Z J Psychiatry*. 1991 Jun;25(2):169-80.
168. Peretti CS, Danion JM, Grange D, Mobarek N. Bilateral ECT and autobiographical memory of subjective experiences related to melancholia: a pilot study. *J Affect Disord*. 1996 Nov 4;41(1):9-15.
169. Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J Ect*. 2001 Dec;17(4):244-53.
170. Pettinati HM, Rosenberg J. Memory self-ratings before and after electroconvulsive therapy: depression-versus ECT induced. *Biol Psychiatry*. 1984 Apr;19(4):539-48.
171. Pisvejc J, Hyrman V, Sikora J, Berankova A, Kobeda B, Auerova M, et al. A comparison of brief and ultrabrief pulse stimuli in unilateral ECT. *J Ect*. 1998 Jun;14(2):68-75.
172. Prakash J, Kotwal A, Prabhu HRA. Therapeutic and Prophylactic Utility of the Memory-Enhancing Drug Donepezil Hydrochloride on Cognition of Patients Undergoing Electroconvulsive Therapy: A Randomized Controlled Trial. *Journal of ECT*. 2006 Sep 2006;22(3):163-8.
173. Pridmore S, Rybak M, Turnier-Shea Y, Reid P, Bruno PR, Couper D. A naturalistic study of response in melancholia to transcranial magnetic stimulation (TMS). *German Journal of Psychiatry*. 1999 1999;2(1):13-21.
174. Prohovnik I, Sackeim HA, Decina P, Malitz S. Acute reductions of regional cerebral blood flow following electroconvulsive therapy. Interactions with modality and time. *Ann N Y Acad Sci*. 1986;462:249-62.
175. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry*. 1996 Aug;153(8):985-92.
176. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry*. 2004 Feb 1;55(3):301-12.
177. Prudic J, Sackeim HA, Decina P, Hopkins N, Ross FR, Malitz S. Acute effects of ECT on cardiovascular functioning: relations to patient and treatment variables. *Acta Psychiatr Scand*. 1987 Apr;75(4):344-51.
178. Prudic J, Sackeim HA, Devanand DP, Krueger RB, Settembrino JM. Acute cognitive effects of subconvulsive electrical stimulation. *Convuls Ther*. 1994 Mar;10(1):4-24.

179. Raes F, Sienaert P, Demyttenaere K, Peuskens J, Williams JMG, Hermans D. Overgeneral memory predicts stability of short-term outcome of electroconvulsive therapy for depression. *Journal of ECT*. 2008;24(1):81-3.
180. Ranjkesh F, Barekatin M, Akuchakian S. Bifrontal versus right unilateral and bitemporal electroconvulsive therapy in major depressive disorder. *J Ect*. 2005 Dec;21(4):207-10.
181. Rasmussen KG, Black JL. Serotonin transporter gene status and electroconvulsive therapy outcomes: a retrospective analysis of 83 patients. *J Clin Psychiatry*. 2009 Jan;70(1):92-4.
182. Rasmussen KG, Mueller M, Knapp RG, Husain MM, Rummans TA, Sampson SM, et al. Antidepressant medication treatment failure does not predict lower remission with ECT for major depressive disorder: A report from the consortium for research in electroconvulsive therapy. *J Clin Psychiatry*. 2007;68(11):1701-6.
183. Rasmussen KG, Snyder KA, Knapp RG, Mueller M, Yim E, Husain MM, et al. Relationship between somatization and remission with ECT. *Psychiatry Res*. 2004 Dec 30;129(3):293-5.
184. Reynaert-Dupuis C, Zdanowicz N, Group AG-BS, Leyman S, Mignon A, Seghers S. Efficacy and tolerance of venlafaxine in depressed patients switched from prior antidepressant treatment. *PRIMARY CARE PSYCHIATRY*. 2002;8:63-8.
185. Rich CL, Spiker DG, Jewell SW. The efficiency of ECT: I. Response rate in depressive episodes. *Psychiatry Research*. 1984;11(3):167-76.
186. Rich CL, Spiker DG, Jewell SW, Neil JF, Phillipson M. ECT response in psychotic versus nonpsychotic unipolar depressives. *J Clin Psychiatry*. 1986 Mar;47(3):123-5.
187. Riddle WJ, Scott AI, Bennie J, Carroll S, Fink G. Current intensity and oxytocin release after electroconvulsive therapy. *Biol Psychiatry*. 1993 Jun 1-15;33(11-12):839-41.
188. Robin A, De Tissera S. A double-blind controlled comparison of the therapeutic effects of low and high energy electroconvulsive therapies. *Br J Psychiatry*. 1982 Oct;141:357-66.
189. Rodger CR, Scott AI, Whalley LJ. Is there a delay in the onset of the antidepressant effect of electroconvulsive therapy? *Br J Psychiatry*. 1994 Jan;164(1):106-9.
190. Roemer RA, Shagass C, Dubin W, Jaffe R, Katz R. Relationship between pretreatment electroencephalographic coherence measures and subsequent response to electroconvulsive therapy: a preliminary study. *Neuropsychobiology*. 1990;24(3):121-4.
191. Rosenberg PB, Mehndiratta RB, Mehndiratta YP, Wamer A, Rosse RB, Balish M. Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *J Neuropsychiatry Clin Neurosci*. 2002 Summer;14(3):270-6.
192. Rossini D, Magri L, Lucca A, Giordani S, Smeraldi E, Zanardi R. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. *J Clin Psychiatry*. 2005 Dec;66(12):1569-75.
193. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005 Sep 1;58(5):355-63.
194. Russell JC, Rasmussen KG, O'Connor MK, Copeman CA, Ryan DA, Rummans TA. Long-term maintenance ECT: A retrospective review of efficacy and cognitive outcome. *Journal of ECT*. 2003 2003;19(1):4-9.
195. Rybak M, Bruno R, Turnier-Shea Y, Pridmore S. An attempt to increase the rate and magnitude of the antidepressant effect of transcranial magnetic stimulation (TMS) a pilot study. *German Journal of Psychiatry*. 2005 2005;8(4):59-65.

196. Sackeim H, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry*. 1987 Apr;44(4):355-60.
197. Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol*. 2007 Dec;10(6):817-26.
198. Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S. Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry*. 1987 Mar;22(3):249-68.
199. Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry*. 2009 Jul;66(7):729-37.
200. Sackeim HA, Freeman J, McElhiney M, Coleman E, Prudic J, Devanand DP. Effects of major depression on estimates of intelligence. *J Clin Exp Neuropsychol*. 1992 Mar;14(2):268-88.
201. Sackeim HA, Keilp JG, Rush AJ, George MS, Marangell LB, Dormer JS, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. *Neuropsychiatry Neuropsychol Behav Neurol*. 2001 Jan;14(1):53-62.
202. Sackeim HA, Lubner B, Moeller JR, Prudic J, Devanand DP, Nobler MS. Electrophysiological correlates of the adverse cognitive effects of electroconvulsive therapy. *J Ect*. 2000 Jun;16(2):110-20.
203. Sackeim HA, Portnoy S, Neeley P. Cognitive consequences of low-dosage electroconvulsive therapy. *Annals of the New York Academy of Sciences*. 1986;VOL. 462:326-40.
204. Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol*. 1990 Apr;10(2):96-104.
205. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med*. 1993 Mar 25;328(12):839-46.
206. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57(5):425-34.
207. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. 2007 Jan;32(1):244-54.
208. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation*. 2008;1(2):71-83.
209. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. 2001 Nov;25(5):713-28.
210. Sanacora G, Fenton LR, Fasula MK, Rothman DL, Levin Y, Krystal JH, et al. Cortical gamma-aminobutyric acid concentrations in depressed patients receiving cognitive behavioral therapy. *Biol Psychiatry*. 2006 Feb 1;59(3):284-6.
211. Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. 2008 May;38(5):651-61.
212. Schule C, Zwanzger P, Baghai T, Mikhael P, Thoma H, Moller HJ, et al. Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: an open follow-up study. *J Psychiatr Res*. 2003 Mar-Apr;37(2):145-53.

213. Scocco P, Frank E. Interpersonal psychotherapy as augmentation treatment in depressed elderly responding poorly to antidepressant drugs: A case series. *Psychotherapy and Psychosomatics*. 2002 Nov-Dec 2002;71(6):357-61.
214. Scott AI, Rodger CR, Stocks RH, Shering AP. Is old-fashioned electroconvulsive therapy more efficacious? A randomised comparative study of bilateral brief-pulse and bilateral sine-wave treatments. *Br J Psychiatry*. 1992 Mar;160:360-4.
215. Scott J, Eccleston D, Boys R. Can we predict the persistence of depression? *Br J Psychiatry*. 1992 Nov;161:633-7.
216. Segman RH, Shapira B, Gorfine M, Lerer B. Onset and time course of antidepressant action: psychopharmacological implications of a controlled trial of electroconvulsive therapy. *Psychopharmacology (Berl)*. 1995 Jun;119(4):440-8.
217. Serra M, Gasto C, Navarro V, Torres X, Blanch J, Masana G. Maintenance electroconvulsive therapy in elderly psychotic unipolar depression. *Medicina Clinica*. 2006;126(13):491-2.
218. Shapira B, Lerer B. Speed of response to bilateral ECT: an examination of possible predictors in two controlled trials. *J Ect*. 1999 Sep;15(3):202-6.
219. Shapira B, Lerer B, Kindler S, Lichtenberg P, Gropp C, Cooper T, et al. Enhanced serotonergic responsivity following electroconvulsive therapy in patients with major depression. *Br J Psychiatry*. 1992 Feb;160:223-9.
220. Shapira B, Tubi N, Drexler H, Lidsky D, Calev A, Lerer B. Cost and benefit in the choice of ECT schedule. Twice versus three times weekly ECT. *Br J Psychiatry*. 1998 Jan;172:44-8.
221. Shapira B, Tubi N, Lerer B. Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J Ect*. 2000 Jun;16(2):97-109.
222. Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijsman HJ, Cowen PJ. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. *J Clin Psychiatry*. 2003 Feb;64(2):192-6.
223. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Ultra-brief pulse ECT in bipolar and unipolar depressive disorder: Differences in speed of response. *Bipolar Disorders*. 2009;11(4):418-24.
224. Sobin C, Prudic J, Devanand DP, Nobler MS, Sackeim HA. Who responds to electroconvulsive therapy? A comparison of effective and ineffective forms of treatment. *Br J Psychiatry*. 1996 Sep;169(3):322-8.
225. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Predictors of retrograde amnesia following ECT. *Am J Psychiatry*. 1995 Jul;152(7):995-1001.
226. Sood N, Treglia M, Obenchain RL, Dulisse B, Melfi CA, Croghan TW. Determinants of antidepressant treatment outcome. *Am J Manag Care*. 2000;6(12):1327-36.
227. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry*. 2000 Dec 2000;48(12):1133-41.
228. Spronk D, Arns M, Bootsma A, van Ruth R, Fitzgerald PB. Long-term effects of left frontal rTMS on EEG and ERPs in patients with depression. *Clin EEG Neurosci*. 2008 Jul;39(3):118-24.
229. Steffens DC, McQuoid DR, Krishnan KR. The Duke Somatic Treatment Algorithm for Geriatric Depression (STAGED) approach. *Psychopharmacol Bull*. 2002 Spring;36(2):58-68.
230. Stek ML, van der Wurff FB, Uitdehaag BMJ, Beekman ATF, Hoogendijk WJG. ECT in the treatment of depressed elderly: lessons from a terminated clinical trial. *International Journal of Geriatric Psychiatry*. 2007;22(10):1052-4.
231. Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. *British Journal of Psychiatry*. 2002;181:284-94.

232. Stoppe A, Louza M, Rosa M, Gil G, Rigonatti S. Fixed high-dose electroconvulsive therapy in the elderly with depression: a double-blind, randomized comparison of efficacy and tolerability between unilateral and bilateral electrode placement. *J Ect*. 2006 Jun;22(2):92-9.
233. Stoudemire A, Hill CD, Dalton ST, Marquardt MG. Rehospitalization rates in older depressed adults after antidepressant and electroconvulsive therapy treatment. *J Am Geriatr Soc*. 1994 Dec;42(12):1282-5.
234. Stoudemire A, Hill CD, Marquardt M, Dalton S, Lewison BJ. Recovery and relapse in geriatric depression after treatment with antidepressants and ECT in a medical-psychiatric population. *Gen Hosp Psychiatry*. 1998 May;20(3):170-4.
235. Stoudemire A, Hill CD, Morris R, Lewison BJ. Long-term outcome of treatment-resistant depression in older adults. *Am J Psychiatry*. 1993 Oct;150(10):1539-40.
236. Stoudemire A, Hill CD, Morris R, Martino-Saltzman D, Markwalter H, Lewison B. Cognitive outcome following tricyclic and electroconvulsive treatment of major depression in the elderly. *Am J Psychiatry*. 1991 Oct;148(10):1336-40.
237. Stoudemire A, Knos G, Gladson M, Markwalter H, Sung YF, Morris R, et al. Labetalol in the control of cardiovascular responses to electroconvulsive therapy in high-risk depressed medical patients. *J Clin Psychiatry*. 1990 Dec;51(12):508-12.
238. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. *Br J Psychiatry*. 1994 Mar;164(3):327-41.
239. Talbot NL, Conwell Y, O'Hara MW, Stuart S, Ward EA, Gamble SA, et al. Interpersonal psychotherapy for depressed women with sexual abuse histories: a pilot study in a community mental health center. *J Nerv Ment Dis*. 2005 Dec;193(12):847-50.
240. Taylor MA, Abrams R. Short-term cognitive effects of unilateral and bilateral ECT. *British Journal of Psychiatry*. 1985;146(MAR.):308-11.
241. Tew JD, Jr., Mulsant BH, Haskett RF, Dolata D, Hixson L, Mann JJ. A randomized comparison of high-charge right unilateral electroconvulsive therapy and bilateral electroconvulsive therapy in older depressed patients who failed to respond to 5 to 8 moderate-charge right unilateral treatments. *J Clin Psychiatry*. 2002 Dec;63(12):1102-5.
242. Tew JD, Jr., Mulsant BH, Haskett RF, Joan P, Begley AE, Sackeim HA. Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. *Ann Clin Psychiatry*. 2007 Jan-Mar;19(1):1-4.
243. Tew JD, Jr., Mulsant BH, Haskett RF, Prudic J, Thase ME, Crowe RR, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. *Am J Psychiatry*. 1999 Dec;156(12):1865-70.
244. Thase ME, Frank E, Mallinger AG, Hamer T, Kupfer DJ. Treatment of imipramine-resistant recurrent depression, III: Efficacy of monoamine oxidase inhibitors. *J Clin Psychiatry*. 1992 Jan;53(1):5-11.
245. Thase ME, Kupfer DJ, Frank E, Jarrett DB. Treatment of imipramine-resistant recurrent depression: II. An open clinical trial of lithium augmentation. *J Clin Psychiatry*. 1989 Nov;50(11):413-7.
246. Thase ME, Reynolds CF, Frank E, Simons AD, et al. Response to cognitive-behavioral therapy in chronic depression. *Journal of Psychotherapy Practice & Research*. 1994 Sum 1994;3(3):204-14.
247. Thase ME, Simons AD, McGeary J, Cahalane JF, Hughes C, Harden T, et al. Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. *American Journal of Psychiatry*. 1992;149(8):1046-52.
248. Thienhaus OJ, Margletta S, Bennett JA. A study of the clinical efficacy of maintenance ECT. *J Clin Psychiatry*. 1990 Apr;51(4):141-4.
249. Triggs WJ, McCoy KJM, Greer R, Rossi F, Bowers D, Kortenkamp S, et al. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biological Psychiatry*. 1999 Jun 1999;45(11):1440-6.

250. Tsuchiyama K, Nagayama H, Yamada K, Isogawa K, Katsuragi S, Kiyota A. Predicting efficacy of electroconvulsive therapy in major depressive disorder. *Psychiatry Clin Neurosci*. 2005 Oct;59(5):546-50.
251. Turnier-Shea Y, Bruno R, Pridmore S. Daily and spaced treatment with transcranial magnetic stimulation in major depression: a pilot study. *Aust N Z J Psychiatry*. 2006 Sep;40(9):759-63.
252. Tutty S, Ludman EJ, Simon G. Feasibility and acceptability of a telephone psychotherapy program for depressed adults treated in primary care. *General Hospital Psychiatry*. 2005 Nov-Dec 2005;27(6):400-10.
253. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Raju TR, Gangadhar BN. Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. *J Affect Disord*. 2007 Dec;104(1-3):231-6.
254. van Beusekom BS, van den Broek WW, Birkenhager TK. Long-term follow-up after successful electroconvulsive therapy for depression: a 4- to 8-year naturalistic follow-up study. *J Ect*. 2007 Mar;23(1):17-20.
255. van den Broek WW, de Lely A, Mulder PG, Birkenhager TK, Buijn JA. Effect of antidepressant medication resistance on short-term response to electroconvulsive therapy. *J Clin Psychopharmacol*. 2004 Aug;24(4):400-3.
256. Vanelle JM, Loo H, Galinowski A, de Carvalho W, Bourdel MC, Brochier P, et al. Maintenance ECT in intractable manic-depressive disorders. *Convuls Ther*. 1994 Sep;10(3):195-205.
257. Vinar O. Tianeptine helps depressed patients resistant to reuptake inhibitors and/or IMAO. *Homeostasis in Health and Disease*. 1999;39 (6):234-5.
258. Vlissides DN, Jenner FA. The response of endogenously and reactivity depressed patients to electroconvulsive therapy. *Br J Psychiatry*. 1982 Sep;141:239-42.
259. Warren EW, Groome DH. Memory test performance under three different waveforms of ECT for depression. *Br J Psychiatry*. 1984 Apr;144:370-5.
260. Watkins E, Scott J, Wingrove J, Rimes K, Bathurst N, Steiner H, et al. Rumination-focused cognitive behaviour therapy for residual depression: a case series. *Behav Res Ther*. 2007 Sep;45(9):2144-54.
261. Welch CA, Weiner RD, Weir D. Efficacy of ECT in the treatment of depression: Wave form and electrode placement considerations. *Psychopharmacology bulletin*. 1982;18(1):31-4.
262. Wesner RB, Winokur G. The influence of age on the natural history of unipolar depression when treated with electroconvulsive therapy. *Eur Arch Psychiatry Neurol Sci*. 1989;238(3):149-54.
263. Williams JH, O'Brien JT, Cullum S. Time course of response to electroconvulsive therapy in elderly depressed subjects. *Int J Geriatr Psychiatry*. 1997 May;12(5):563-6.
264. Wu L, Zou H, Zhou Q, Liu Z, Cheng B. Preemptive analgesia with butorphanol in psychotic patients following modified electroconvulsive therapy: A randomized controlled trial. *Neural Regeneration Research*. 2008;3(1):75-8.
265. Yildiz A, Mantar A, Simsek S, Onur E, Gokmen N, Fidaner H. Combination of pharmacotherapy with electroconvulsive therapy in prevention of depressive relapse: a pilot controlled trial. *J ECT*. 2010 Jun;26(2):104-10.
266. Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, et al. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *J Affect Disord*. 2006 Mar;91(1):83-6.
267. Zielinski RJ, Roose SP, Devanand DP, Woodring S, Sackeim HA. Cardiovascular complications of ECT in depressed patients with cardiac disease. *Am J Psychiatry*. 1993 Jun;150(6):904-9.
268. Zimmerman M, Coryell W, Pfohl B, Corenthal C, Stangl D. ECT response in depressed patients with and without a DSM-III personality disorder. *Am J Psychiatry*. 1986 Aug;143(8):1030-2.

269. Zorumski CF, Rutherford JL, Burke WJ, Reich T. ECT in primary and secondary depression. *J Clin Psychiatry*. 1986 Jun;47(6):298-300.

Wrong Population

1. Aarre TF, Dahl AA, Johansen JB, Kjonniksen I, Neckelmann D. Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence. *Nord J Psychiatry*. 2003;57(3):227-32.
2. Abbass Allan A, Hancock Jeffrey T, Henderson J, Kisely Steve R. Short-term psychodynamic psychotherapies for common mental disorders. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd 2006.
3. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci*. 2005 Dec;255(6):387-400.
4. Anderson B, Mishory A, Nahas Z, Borckardt JJ, Yamanaka K, Rastogi K, et al. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *Journal of ECT*. 2006;22(1):49-53.
5. Anderson IM, Delvai NA, Ashim B, Ashim S, Lewin C, Singh V, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. *Br J Psychiatry*. 2007 Jun;190:533-4.
6. Armitage R, Husain M, Hoffmann R, Rush AJ. The effects of vagus nerve stimulation on sleep EEG in depression: a preliminary report. *J Psychosom Res*. 2003 May;54(5):475-82.
7. Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis*. 1999 Feb;187(2):114-7.
8. Baeken C, Leyman L, De Raedt R, Vanderhasselt MA, D'Haenen H. Lack of impact of repetitive high frequency transcranial magnetic stimulation on mood in healthy female subjects. *Journal of Affective Disorders*. 2006 Jan 2006;90(1):63-6.
9. Bagadia VN, Shah LP, Pradhan PV. Evaluation of cognitive effects of ECT (preliminary observations). *Indian J Psychiatry*. 1981;23(4):324-9.
10. Bagby RM, Quilty LC, Segal ZV, McBride CC, Kennedy SH, Costa PT. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. *Can J Psychiatry*. 2008 Jun;53(6):361-70.
11. Baldomero EB, Ubago JG, Cercos CL, Ruiloba JV, Calvo CG, Lopez RP. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depress Anxiety*. 2005 Aug 10;22(2):68-76.
12. Bares M, Kopecek M, Novak T, Stopkova P, Sos P, Kozeny J, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: A double-blind, single-centre, randomized study. *Journal of Affective Disorders*. 2009 11;118(1):94-100.
13. Bauer M, Adli M, Baethge C, Berghofer A, Sasse J, Heinz A, et al. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. *Can J Psychiatry*. 2003 Aug;48(7):440-8.
14. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol*. 1999 Oct;19(5):427-34.

15. Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfmer S, et al. Lithium augmentation therapy in refractory depression-update 2002. *Eur Arch Psychiatry Clin Neurosci*. 2003 Jun;253(3):132-9.
16. Bauer M, Tharmanathan P, Volz HP, Moeller HJ, Freemantle N. The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: a meta-analysis. *Eur Arch Psychiatry Clin Neurosci*. 2009 Apr;259(3):172-85.
17. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol*. 1996 Aug;16(4):307-14.
18. Birkenhager TK, van den Broek WW, Mulder PG, Buijn JA, Moleman P. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. *J Clin Psychiatry*. 2004 Nov;65(11):1505-10.
19. Black DW, Winokur G, Mohandoss E, Woolson RF, Nasrallah A. Does treatment influence mortality in depressives? A follow-up of 1076 patients with major affective disorders. *Annals of Clinical Psychiatry*. 1989;1(3):165-73.
20. Black DW, Winokur G, Nasrallah A. Treatment and outcome in secondary depression: a naturalistic study of 1087 patients. *J Clin Psychiatry*. 1987 Nov;48(11):438-41.
21. Black DW, Winokur G, Nasrallah A. The treatment of depression: electroconvulsive therapy v antidepressants: a naturalistic evaluation of 1,495 patients. *Compr Psychiatry*. 1987 Mar-Apr;28(2):169-82.
22. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. *Br J Psychiatry*. 1997 Oct;171:328-34.
23. Boggio PS, Bermanpohl F, Vergara AO, Muniz ALCR, Nahas FH, Leme PB, et al. Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *Journal of Affective Disorders*. 2007 Aug 2007;101(1):91-8.
24. Boggio PS, Fregni F, Bermanpohl F, Mansur CG, Rosa M, Rumi DO, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Mov Disord*. 2005 Sep;20(9):1178-84.
25. Bonne O, Krausz Y, Shapira B, Bocher M, Karger H, Gorfine M, et al. Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy. *Journal of Nuclear Medicine*. 1996;37(7):1075-80.
26. Bradvik L, Berglund M. Long-term treatment and suicidal behavior in severe depression: ECT and antidepressant pharmacotherapy may have different effects on the occurrence and seriousness of suicide attempts. *Depress Anxiety*. 2006;23(1):34-41.
27. Brakemeier EL, Wilbertz G, Rodax S, Danker-Hopfe H, Zinka B, Zwanzger P, et al. Patterns of response to repetitive transcranial magnetic stimulation (rTMS) in major depression: replication study in drug-free patients. *J Affect Disord*. 2008 May;108(1-2):59-70.
28. Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. *Br Med J (Clin Res Ed)*. 1984 Jan 7;288(6410):22-5.
29. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial. *Journal of the American Medical Association*. 2008 Feb 2008;299(8):901-13.
30. Browne M, Lapierre YD, Hrdina PD, Horn E. Lithium as an adjunct in the treatment of major depression. *Int Clin Psychopharmacol*. 1990 Apr;5(2):103-10.

31. Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy (Provisional abstract). *Acta Psychiatrica Scandinavica* 2010;174-9.
32. Bschor T, Bauer M. Efficacy and mechanisms of action of lithium augmentation in refractory major depression. *Curr Pharm Des.* 2006;12(23):2985-92.
33. Burke MJ, Husain MM. Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. *J Ect.* 2006 Sep;22(3):218-22.
34. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: A meta-analysis. *International Journal of Neuropsychopharmacology.* 2002;5(1):73-103.
35. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICH) study. *Psychosom Med.* 2004 Jul-Aug;66(4):466-74.
36. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry.* 2002 Jan 15;51(2):183-8.
37. Carretero B, Martin MJ, Juan A, Pradana ML, Martin B, Carral M, et al. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med.* 2009 May-Jun;10(4):748-53.
38. Cassano GB, Jori MC. Efficacy and safety of amisulpride 50 mg versus paroxetine 20 mg in major depression: A randomized, double-blind, parallel group study. *International Clinical Psychopharmacology.* 2002;17(1):27-32.
39. Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, et al. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. *Int J Neuropsychopharmacol.* 2005 Jun;8(2):223-33.
40. Cipriani A, Smith K, Burgess S, Carney S, Goodwin G, Geddes J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. *Cochrane Database Syst Rev.* 2006(4):CD003492.
41. Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. *Biological Psychiatry.* 1995;37(11):777-88.
42. Conca A, Koppi S, König P, Swoboda E, Krecke N. Transcranial magnetic stimulation: a novel antidepressive strategy? *Neuropsychobiology.* 1996;34(4):204-7.
43. Cook IA, Leuchter AF, Witte E, Abrams M, Uijtdehaage SH, Stubbeman W, et al. Neurophysiologic predictors of treatment response to fluoxetine in major depression. *Psychiatry Res.* 1999 Mar 22;85(3):263-73.
44. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: A systematic review and meta-analysis. *J Psychiatry Neurosci.* 2005;30(2):83-90.
45. Craig TJ, Grossman S, Bromet EJ, Fochtmann LJ, Carlson GA. Medication use patterns and two-year outcome in first-admission patients with major depressive disorder with psychotic features. *Compr Psychiatry.* 2007 Nov-Dec;48(6):497-503.
46. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry.* 2007 Jun;68(6):935-40.
47. Dannon PN, Schreiber S, Dolberg OT, Shemer L, Grunhaus L. Transcranial magnetic stimulation is effective in the treatment of relapse of depression. *International Journal of Psychiatry in Clinical Practice.* 2000;4(3):223-6.

48. Dejonge P, Honig A, Van Melle JP, Schene AH, Kuyper AMG, Tulner D, et al. Nonresponse to treatment for depression following myocardial infarction: Association with subsequent cardiac events. *The American Journal of Psychiatry*. 2007 09;164(9):1371-8.
49. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, Pearlman C, Stern WM, Thall M, et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry*. 2008 Jun;69(6):930-4.
50. DeRubeis RJ, Feeley M. Determinants of change in cognitive therapy for depression. *Cognitive Therapy and Research*. 1990;14(5):469-82.
51. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. *American Journal of Psychiatry*. 1999;156(7):1007-13.
52. Devinsky O, Duchowny MS. Seizures after convulsive therapy: a retrospective case survey. *Neurology*. 1983 Jul;33(7):921-5.
53. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol*. 1998 Dec;18(6):465-9.
54. Dinan TG, Barry S. A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. *Acta Psychiatr Scand*. 1989 Jul;80(1):97-100.
55. Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *Journal of Pharmacology and Experimental Therapeutics*. 2006;318(2):890-8.
56. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med*. 2008 May;38(5):611-23.
57. Evans MD, Hollon SD, DeRubeis RJ, Piasecki JM, Grove WM, Garvey MJ, et al. Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of General Psychiatry*. 1992;49(10):802-8.
58. Evers S, Hangst K, Pecuch PW. The impact of repetitive transcranial magnetic stimulation on pituitary hormone levels and cortisol in healthy subjects. *Journal of Affective Disorders*. 2001 Sep 2001;66(1):83-8.
59. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. *Journal of Clinical Psychopharmacology*. 2002 08;22(4):379-87.
60. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry*. 1994 Sep;151(9):1372-4.
61. Feinsod M, Kreinin B, Chistyakov A, Klein E. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depression and Anxiety*. 1998;7(2):65-8.
62. Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. *Acta Psychiatr Scand*. 2001 Jan;103(1):66-72.
63. Fink M, Rush AJ, Knapp R, Rasmussen K, Mueller M, Rummans TA, et al. DSM melancholic features are unreliable predictors of ECT response: a CORE publication. *J Ect*. 2007 Sep;23(3):139-46.
64. Flint AJ, Rifat SL. The treatment of psychotic depression in later life: a comparison of pharmacotherapy and ECT. *Int J Geriatr Psychiatry*. 1998 Jan;13(1):23-8.
65. Flint AJ, Rifat SL. Two-year outcome of psychotic depression in late life. *Am J Psychiatry*. 1998 Feb;155(2):178-83.

66. Floyd M, Scogin F, McKendree-Smith NL, Floyd DL, Rokke PD. Cognitive therapy for depression: a comparison of individual psychotherapy and bibliotherapy for depressed older adults. *Behavior Modification*. 2004;28(2):297-318.
67. Freeman CP, Weeks D, Kendell RE. ECT: II: patients who complain. *Br J Psychiatry*. 1980 Jul;137:17-25.
68. Fregni F, Ono CR, Santos CM, Bermpohl F, Buchpiguel C, Barbosa ER, et al. Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion in PD. *Neurology*. 2006 Jun 13;66(11):1629-37.
69. Fregni F, Santos CM, Myczkowski ML, Rigolino R, Gallucci-Neto J, Barbosa ER, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004 Aug;75(8):1171-4.
70. Gallagher DE, Thompson LW. Treatment of major depressive disorder in older adult outpatients with brief psychotherapies. *Psychotherapy*. 1982;19(4):482-90.
71. Gangadhar BN, Kapur RL, Kalyanasundaram S. Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. *Br J Psychiatry*. 1982 Oct;141:367-71.
72. Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, MicÃ³ J, Ibarra O, et al. Prefrontal repetitive transcranial magnetic stimulation as add on treatment for depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2001 Oct 2001;71(4):546-8.
73. Geddes J, Carney S, Cowen P, Goodwin G, Rogers R, Dearnness K, et al. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003 Mar 8;361(9360):799-808.
74. George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li X-B, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry*. 2000 Nov 2000;48(10):962-70.
75. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord*. 1998 Apr;49(1):59-72.
76. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*. 2007 Sep;116(3):165-73.
77. Grunhaus L, Dolberg OT, Polak D, Dannon PN. Monitoring the response to rTMS in depression with visual analog scales. *Human Psychopharmacology: Clinical and Experimental*. 2002 Oct 2002;17(7):349-52.
78. Grunhaus L, Polak D, Amiaz R, Dannon PN. Motor-evoked potential amplitudes elicited by transcranial magnetic stimulation do not differentiate between patients and normal controls. *Int J Neuropsychopharmacol*. 2003 Dec;6(4):371-8.
79. Hansen PE, Videbech P, Clemmensen K, Sturlason R, Jensen HM, Vestergaard P. Repetitive transcranial magnetic stimulation as add-on antidepressant treatment. The applicability of the method in a clinical setting. *Nord J Psychiatry*. 2004;58(6):455-7.
80. Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler K, Lechner T, et al. No benefit derived from repetitive transcranial magnetic stimulation in depression: A prospective, single centre, randomised, double blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery and Psychiatry*. 2004;75(2):320-2.
81. Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, et al. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *Journal of Clinical Psychiatry*. 2004 Jun 2004;65(6):772-82.

82. Heijnen WT, van den Broek WW, Birkenhager TK. Treatment failure with a tricyclic antidepressant followed by lithium addition and response to subsequent electroconvulsive therapy. *J Clin Psychiatry*. 2008 Dec;69(12):1887-91.
83. Henry ME, Schmidt ME, Matochik JA, Stoddard EP, Potter WZ. The effects of ECT on brain glucose: a pilot FDG PET study. *J Ect*. 2001 Mar;17(1):33-40.
84. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RAE, Faber TL, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology*. 1999;52(6):1166-73.
85. Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review (Structured abstract). *Journal of Clinical Psychiatry*. 2006(12):1870-6.
86. Hoepfner J, Padberg F, Domes G, Zinke A, Herpertz SC, Grossheinrich N, et al. Influence of repetitive transcranial magnetic stimulation on psychomotor symptoms in major depression. *Eur Arch Psychiatry Clin Neurosci*. 2010 Apr;260(3):197-202.
87. Holtzheimer 3rd PE, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacology bulletin*. 2001;35(4):149-69.
88. Höppner J, Schulz M, Irmisch G, Mau R, Schläfke D, Richter J. Antidepressant efficacy of two different rTMS procedures: High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. *European Archives of Psychiatry and Clinical Neuroscience*. 2003 2003;253(2):103-9.
89. Ikeji OC, Ohaeri JU, Osahon RO, Agidee RO. Naturalistic comparative study of outcome and cognitive effects of unmodified electro-convulsive therapy in schizophrenia, mania and severe depression in Nigeria. *East Afr Med J*. 1999 Nov;76(11):644-50.
90. Janakiramaiah N, Gangadhar BN, Naga Venkatesha Murthy PJ, Harish MG, Subbakrishna DK, Vedomurthachar A. Antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in melancholia: a randomized comparison with electroconvulsive therapy (ECT) and imipramine. *J Affect Disord*. 2000 Jan-Mar;57(1-3):255-9.
91. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry*. 2002 Apr 15;51(8):659-67.
92. Joffe RT, Singer W, Levitt AJ, MacDonald C. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry*. 1993 May;50(5):387-93.
93. Joseph MH, Risby D, Crow TJ, Deakin JF, Johnstone EC, Lawler P. MHPG excretion in endogenous depression: relationship to clinical state and the effects of ECT. *Psychopharmacology (Berl)*. 1985;87(4):442-8.
94. Kalb R, Ellinger K, Reulbach U. Improvement in response times for simple and complex tasks after electroconvulsive therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003 May;27(3):459-65.
95. Kapstan A, Yaroslavsky Y, Applebaum J, Belmaker RH, Grisaru N. Right prefrontal TMS versus sham treatment of mania: A controlled study. *Bipolar Disorders*. 2003 Feb 2003;5(1):36-9.
96. Katona CLE, Abou-Saleh MT, Harrison DA, Nairac BA. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry*. 1995 01;166:80-6.
97. Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, et al. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. *Journal of Psychiatric Research*. Netherlands: Elsevier Science 2009:205-14.

98. Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RMA, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry*. 1992;49(10):809-16.
99. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine*. 2000;342(20):1462-70.
100. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 2006;1337-44.
101. Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry*. 2002 Mar;63(3):181-6.
102. Kennedy SH, Segal ZV, Cohen NL, Levitan RD, Gemar M, Bagby RM. Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: An exploratory trial. *Journal of Clinical Psychiatry*. 2003 Apr 2003;64(4):439-44.
103. Khalid N, Atkins M, Tredget J, Giles M, Champney-Smith K, Kirov G. The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. *J Ect*. 2008 Jun;24(2):141-5.
104. Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. *J Ect*. 2003 Sep;19(3):139-47.
105. Kito S, Fujita K, Koga Y. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. *Neuropsychobiology*. 2008;58(1):29-36.
106. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry*. 1999 Apr;56(4):315-20.
107. Kocsis JH, Friedman RA, Markowitz JC, Leon AC, Miller NL, Gniwesch L, et al. Maintenance therapy for chronic depression: A controlled clinical trial of desipramine. *Archives of General Psychiatry*. 1996;53(9):769-76.
108. Koerselman F, Laman DM, van Duijn H, van Duijn MA, Willems MA. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *J Clin Psychiatry*. 2004 Oct;65(10):1323-8.
109. Kok RM, Vink D, Heeren TJ, Nolen WA. Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open, randomized, controlled trial. *J Clin Psychiatry*. 2007 Aug;68(8):1177-85.
110. Kolbinger HM, Höflich G, Hufnagel A, Möller H-J, Kasper S. Transcranial magnetic stimulation (TMS) in the treatment of major depression: A pilot study. *Human Psychopharmacology: Clinical and Experimental*. 1995 Jul-Aug 1995;10(4):305-10.
111. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002;8(5):270-5.
112. Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2000 Sum 2000;12(3):376-84.

113. Kroessler D. Relative efficacy rates for therapies of delusional depression. *Convulsive Therapy*. 1985;1(3):173-82.
114. Laidlaw K, Davidson K, Toner H, Jackson G, Clark S, Law J, et al. A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *Int J Geriatr Psychiatry*. 2008 Aug;23(8):843-50.
115. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2008;53(9):621.
116. Landén M, Björling G, Agren H, Fahlén T. A randomized, double-blind, placebo-controlled trial of busiprone in combination with an SSRI in patients with treatment-refractory depression. *Journal of Clinical Psychiatry*. 1998 12;59(12):664-8.
117. Landreville P, Bissonnette L. Effects of cognitive bibliotherapy for depressed older adults with a disability. *Clinical Gerontologist*. 1997 1997;17(4):35-55.
118. Langguth B, Wiegand R, Kharraz A, Landgrebe M, Marienhagen J, Frick U, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinol Lett*. 2007 Oct;28(5):633-8.
119. Lefaucheur JP, Lucas B, Andraud F, Hogrel JY, Bellivier F, Del Cul A, et al. Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation. *J Psychiatr Res*. 2008 Apr;42(5):389-98.
120. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. *JAMA*. 2008/10/02 ed 2008;1551-65.
121. Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *J Consult Clin Psychol*. 2007 Apr;75(2):267-76.
122. Licht RW, Qvitzau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. *Psychopharmacology (Berl)*. 2002 May;161(2):143-51.
123. Lincoln NB, Flannaghan T. Cognitive behavioral psychotherapy for depression following stroke: A randomized controlled trial. *Stroke*. 2003;34(1):111-5.
124. Linsen AC, Zitman FG. Patient evaluation of a cognitive behavioral group program for patients with chronic low back pain. *Social Science & Medicine*. 1984 1984;19(12):1361-5.
125. Lisanby SH, Sampson S, Husain MM, Petrides G, Knapp RG, McCall V, et al. Toward individualized post-electroconvulsive therapy care: piloting the Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE) intervention. *Journal of ECT*. 2008 Sep 2008;24(3):179-82.
126. Loo C, Mitchell P, Sachdev P, McDermont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *American Journal of Psychiatry*. 1999 Jun 1999;156(6):946-8.
127. Loo C, Sachdev P, Elsayed H, McDermont B, Mitchell P, Wilkinson M, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry*. 2001 Apr 1;49(7):615-23.
128. Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol Med*. 2003 Jan;33(1):33-40.
129. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. *Psychol Med*. 2007 Mar;37(3):341-9.

130. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Archives of General Psychiatry*. 2003;60(7):737-46.
131. Maes M, Libbrecht I, van Hunsel F, Campens D, Meltzer HY. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J Clin Psychopharmacol*. 1999 Apr;19(2):177-82.
132. Maihofner C, Ropohl A, Reulbach U, Hiller M, Elstner S, Kornhuber J, et al. Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study. *Neuroreport*. 2005 Nov 7;16(16):1839-42.
133. Marangell LB, Suppes T, Zboyan HA, Prasad SJ, Fischer G, Snow D, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry*. 2008 Feb;69(2):183-9.
134. Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, Ramanujam S, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. *J Clin Psychiatry*. 2007 Apr;68(4):512-7.
135. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry*. 2003 Jun;182:480-91.
136. McCall WV, Prudic J, Olfson M, Sackeim H. Health-related quality of life following ECT in a large community sample. *J Affect Disord*. 2006 Feb;90(2-3):269-74.
137. McGrath PJ, Stewart JW, Nunes EV, Ocepek-Welickson K, Rabkin JG, Quitkin FM, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry*. 1993 Jan;150(1):118-23.
138. Menkes DL, Bodnar P, Ballesteros RA, Swenson MR. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: A case-control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery & Psychiatry*. 1999 Jul 1999;67(1):113-5.
139. Mingli H, Zhengtian G, Xinyi W, Xiaoping T. Effects of repetitive transcranial magnetic stimulation on hypothalamic-pituitary-adrenal axis of patients with depression. *Journal of Medical Colleges of PLA*. 2009 December;24(6):337-45.
140. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry*. 2005 Sep;162(9):1588-601.
141. Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol Med*. 2008 Mar;38(3):323-33.
142. Moller AL, Hjaltason O, Ivarsson O, Stefansson SB. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P(300) event-related potential. *Nord J Psychiatry*. 2006;60(4):282-5.
143. Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Muri RM, Berkhoff M, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res*. 2004 Apr 30;126(2):123-33.
144. Münchau A, Langosch JM, Gerschlager W, Rothwell JC, Orth M, Trimble MR. Mirtazapine increases cortical excitability in healthy controls and epilepsy patients with major depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2005 Apr 2005;76(4):527-33.

145. Murray G, Michalak EE, Axler A, Yaxley D, Hayashi B, Westrin A, et al. Relief of Chronic or Resistant Depression (Re-ChORD): A pragmatic, randomized, open-treatment trial of an integrative program intervention for chronic depression. *Journal of Affective Disorders*. 2010 June;123(1-3):243-8.
146. Nahas Z, DeBrux C, Chandler V, Lorberbaum JP, Speer AM, Molloy MA, et al. Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *J Ect*. 2000 Dec;16(4):380-90.
147. Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord*. 2003 Feb;5(1):40-7.
148. Nahas Z, Teneback CC, Kozel A, Speer AM, DeBrux C, Molloy M, et al. Brain effects of TMS delivered over prefrontal cortex in depressed adults: Role of stimulation frequency and coil-cortex distance. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2001 Fal 2001;13(4):459-70.
149. Navarro V, Gasto C, Lomena F, Mateos JJ, Portella MJ, Masana G, et al. No brain perfusion impairment at long-term follow-up in elderly patients treated with electroconvulsive therapy for major depression. *J Ect*. 2004 Jun;20(2):89-93.
150. Navarro V, Gasto C, Torres X, Masana G, Penades R, Guarch J, et al. Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. *Am J Geriatr Psychiatry*. 2008 Jun;16(6):498-505.
151. Nelson JC, Mazure CM, Jatlow PI, Bowers MB, Jr., Price LH. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry*. 2004 Feb 1;55(3):296-300.
152. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials (Structured abstract). *American Journal of Psychiatry* 2009:980-91.
153. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci U S A*. 2003/11/15 ed 2003:14293-6.
154. Nierenberg AA, Trivedi MH, Gaynes BN, Mitchell J, Davis LL, Husain MM, et al. Effectiveness study of venlafaxine-XR combined with aripiprazole for chronic or recurrent major depressive disorder. *Australian and New Zealand Journal of Psychiatry*. 2009;43 (10):956-67.
155. O'Connor MG, Jerskey BA, Robertson EM, Brenninkmeyer C, Ozdemir E, Leone AP. The effects of repetitive transcranial magnetic stimulation (rTMS) on procedural memory and dysphoric mood in patients with major depressive disorder. *Cogn Behav Neurol*. 2005 Dec;18(4):223-7.
156. Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhael P, Ella R, et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology*. 2002 Oct;27(4):638-45.
157. Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: A [18F]-fluorodeoxyglucose PET and MRI study. *International Journal of Neuropsychopharmacology* 2010:45-59.
158. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study. *Movement Disorders*. 2010 October;25 (14):2311-7.

159. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008 Apr 1;63(7):699-704.
160. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry*. 2007 Jun;68(6):826-31.
161. Pardo JV, Sheikh SA, Schwindt GC, Lee JT, Kuskowski MA, Surerus C, et al. Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism. *Neuroimage*. 2008 Aug 15;42(2):879-89.
162. Parker G, Roy K, Hadzi-Pavlovic D, Pedic F. Psychotic (delusional) depression: A meta-analysis of physical treatments. *Journal of Affective Disorders*. 1992;24(1):17-24.
163. Parker G, Roy K, Wilhelm K, Mitchell P. Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *J Clin Psychiatry*. 2001 Feb;62(2):117-25.
164. Patkar AA, Masand PS, Pae C-U, Peindl K, Hooper-Wood C, Mannelli P, et al. A Randomized, Double-blind, Placebo-controlled Trial of Augmentation with an Extended Release Formulation of Methylphenidate in Outpatients with Treatment-Resistant Depression. *Journal of Clinical Psychopharmacology*. 2006 12;26(6):653-6.
165. Paul SM, Extein I, Calil HM. Use of ECT with treatment-resistant depressed patients at the National Institute of Mental Health. *American Journal of Psychiatry*. 1981;138(4):486-9.
166. Perry PJ, Morgan DE, Smith RE, Tsuang MT. Treatment of unipolar depression accompanied by delusions. ECT versus tricyclic antidepressant-antipsychotic combinations. *J Affect Disord*. 1982 Sep;4(3):195-200.
167. Peselow ED, Filippi AM, Goodnick P, Barouche F, Fieve RR. The short- and long-term efficacy of paroxetine HCl: B. Data from a double-blind crossover study and from a year-long term trial vs. imipramine and placebo. *Psychopharmacol Bull*. 1989/01/01 ed 1989:272-6.
168. Peselow ED, Filippi AM, Goodnick P, Barouche F, Fieve RR. The short- and long-term efficacy of paroxetine HCl: A. Data from a 6-week double-blind parallel design trial vs. imipramine and placebo. *Psychopharmacol Bull*. 1989;25(2):267-71.
169. Peterson TJ, Feldman G, Harley R, Fresco DM, Graves L, Holmes A, et al. Extreme response style in recurrent and chronically depressed patients: Change with antidepressant administration and stability during continuation treatment. *Journal of Consulting and Clinical Psychology*. 2007 Feb 2007;75(1):145-53.
170. Philibert RA, Richards L, Lynch CF, Winokur G. Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. *Journal of Clinical Psychiatry*. 1995;56(7 SUPPL.):390-4.
171. Pogarell O, Koch W, Pöpperl G, Tatsch K, Jakob F, Zwanzger P, et al. Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: preliminary results of a dynamic [¹²³I] IBZM SPECT study. *Journal of Psychiatric Research*. 2006 Jun 2006;40(4):307-14.
172. Poulet E, Brunelin J, Boeuvre C, Lerond J, D'Amato T, Dalery J, et al. Repetitive transcranial magnetic stimulation does not potentiate antidepressant treatment. *Eur Psychiatry*. 2004 Sep;19(6):382-3.
173. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology*. 2000 Jun 2000;3(2):129-34.
174. Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research*. 1990;31(3):287-96.

175. Quilty LC, De Fruyt F, Rolland JP, Kennedy SH, Rouillon PF, Bagby RM. Dimensional personality traits and treatment outcome in patients with major depressive disorder. *J Affect Disord.* 2008 Jun;108(3):241-50.
176. Rami L, Goti J, Ferrer J, Marcos T, Salamero M, Bernardo M. Cognitive functions after only one ECT session: a controlled study. *Psychiatry Res.* 2008 Apr 15;158(3):389-94.
177. Rasmussen KG, Knapp RG, Biggs MM, Smith GE, Rummans TA, Petrides G, et al. Data management and design issues in an unmasked randomized trial of electroconvulsive therapy for relapse prevention of severe depression: the consortium for research in electroconvulsive therapy trial. *J Ect.* 2007 Dec;23(4):244-50.
178. Reimherr F, Amsterdam J, Dunner D, Adler L, Zhang S, Williams D, et al. Genetic polymorphisms in the treatment of depression: speculations from an augmentation study using atomoxetine. *Psychiatry Res.* 2010 Jan 30;175(1-2):67-73.
179. Reynolds, III, C. F., Frank E, Houck PR, Mazumdar S, Dew MA, Cornes C, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *American Journal of Psychiatry.* 1997;154(7):958-62.
180. Reynolds, III, C. F., Frank E, Kupfer DJ, Thase ME, Perel JM, Mazumdar S, et al. Treatment outcome in recurrent major depression: A post hoc comparison of elderly ('young old') and midlife patients. *American Journal of Psychiatry.* 1996;153(10):1288-92.
181. Reynolds, III, C. F., Miller MD, Pasternak RE, Frank E, Perel JM, Cornes C, et al. Treatment of bereavement-related major depressive episodes in later life: A controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *American Journal of Psychiatry.* 1999;156(2):202-8.
182. Reynolds I, C. F., Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression. A randomized controlled trial in patients older than 59 years. *Journal of the American Medical Association.* 1999;281(1):39-45.
183. Reynolds I, C. F., Frank E, Perel JM, Miller MD, Cornes C, Rifai AH, et al. Treatment of consecutive episodes of major depression in the elderly. *American Journal of Psychiatry.* 1994;151(12):1740-3.
184. Rodriguez-Martin José L, Barbanoj José M, Schlaepfer TE, Clos Susana SC, Pérez V, Kulisevsky J, et al. Transcranial magnetic stimulation for treating depression. *Cochrane Database of Systematic Reviews.* Chichester, UK: John Wiley & Sons, Ltd 2001.
185. Rollnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengler R, et al. High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. *Neuroreport: For Rapid Communication of Neuroscience Research.* 2000 Dec 2000;11(18):4013-5.
186. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res.* 2005 Nov 15;137(1-2):1-10.
187. Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Andersen SW, Van Campen LE, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol.* 2004 Aug;24(4):365-73.
188. Rubin EH, Kinscherf DA, Figiel GS, Zorumski CF. The nature and time course of cognitive side effects during electroconvulsive therapy in the elderly. *J Geriatr Psychiatry Neurol.* 1993 Apr-Jun;6(2):78-83.
189. Ruhe HG, Huyser J, Swinkels JA, Schene AH. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *J Clin Psychiatry.* 2006 Dec;67(12):1836-55.

190. Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry*. 2005 Jan 15;57(2):162-6.
191. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biological Psychiatry*. 2000;47(4):276-86.
192. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med*. 2006 Mar 23;354(12):1231-42.
193. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Jama*. 2001 Mar 14;285(10):1299-307.
194. Salinsky MC. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology*. 1995;45(2):224-30.
195. Schat A, van den Broek WW, Mulder PG, Birkenhager TK, van Tuijl R, Murre JM. Changes in everyday and semantic memory function after electroconvulsive therapy for unipolar depression. *J Ect*. 2007 Sep;23(3):153-7.
196. Schatzberg AF, Rush AJ, Arnow BA, Banks PL, Blalock JA, Borian FE, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch Gen Psychiatry*. 2005 May;62(5):513-20.
197. Schneider LS, Sloane RB, Staples FR, Bender M. Pretreatment orthostatic hypotension as a predictor of response to nortriptyline in geriatric depression. *Journal of Clinical Psychopharmacology*. 1986;6(3):172-6.
198. Schopf J, Baumann P, Lemarchand T, Rey M. Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Results of a placebo-controlled double-blind study. *Pharmacopsychiatry*. 1989 Sep;22(5):183-7.
199. Schuster P, Opgenoorth E, Gabriel E, Presslich O, Sowinetz B. Results of learning experiments in the course of treatment of endogenous depression. A comparison of electroconvulsive and pharmacological treatment. *Psychopathology*. 1986;19(3):116-30.
200. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. 2009 Jan;39(1):65-75.
201. Schutter DJLG, Martin Laman D, Van Honk J, Vergouwen AC, Frank Koerselman G. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. *International Journal of Neuropsychopharmacology*. 2009 June;12(5):643-50.
202. Schutter DJLG, van Honk J, Laman M, Vergouwen AC, Koerselman F. Increased sensitivity for angry faces in depressive disorder following 2 weeks of 2-Hz repetitive transcranial magnetic stimulation to the right parietal cortex. *International Journal of Neuropsychopharmacology*. 2010;13(9):1155-61.
203. Scott AIF, Freeman CPL. Edinburgh primary care depression study: Treatment outcome, patient satisfaction, and cost after 16 weeks. *British Medical Journal*. 1992;304(6831):883-7.
204. Shapira B, Gorfine M, Lerer B. A prospective study of lithium continuation therapy in depressed patients who have responded to electroconvulsive therapy. *Convuls Ther*. 1995 Jun;11(2):80-5.
205. Shiah IS, Yatham LN, Srisurapanont M, Lam RW, Tam EM, Zis AP. Does the addition of pindolol accelerate the response to electroconvulsive therapy in patients with major depression? A double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol*. 2000 Jun;20(3):373-8.

206. Smith GE, Rasmussen KG, Jr., Cullum CM, Felmlee-Devine MD, Petrides G, Rummans TA, et al. A randomized controlled trial comparing the memory effects of continuation electroconvulsive therapy versus continuation pharmacotherapy: results from the Consortium for Research in ECT (CORE) study. *J Clin Psychiatry*. 2010 Feb;71(2):185-93.
207. Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry*. 2007 Jul;15(7):553-63.
208. Souza FG, Goodwin GM. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. *Br J Psychiatry*. 1991 May;158:666-75.
209. Spalletta G, Guida G, Caltagirone C. Is left stroke a risk-factor for selective serotonin reuptake inhibitor antidepressant treatment resistance? *J Neurol*. 2003 Apr;250(4):449-55.
210. Speer AM, Repella JD, Figueras S, Demian NK, Kimbrell TA, Wasserman EM, et al. Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *J Ect*. 2001 Dec;17(4):259-63.
211. Squire LR, Slater PC. Electroconvulsive therapy and complaints of memory dysfunction: a prospective three-year follow-up study. *Br J Psychiatry*. 1983 Jan;142:1-8.
212. Stain-Malmgren R, Khoury AE, Aberg-Wistedt A, Tham A. Serotonergic function in major depression and effect of sertraline and paroxetine treatment. *Int Clin Psychopharmacol*. 2001 Mar;16(2):93-101.
213. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *Br J Psychiatry*. 1993 May;162:634-40.
214. Stek ML, Van der Wurff FB, Hoogendijk WL, Beekman AT. Electroconvulsive therapy for the depressed elderly. *Cochrane Database Syst Rev*. 2003(2):CD003593.
215. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. *J Clin Psychiatry*. 1983 May;44(5 Pt 2):148-52.
216. Stewart JW, McGrath PJ, Quitkin FM. Do age of onset and course of illness predict different treatment outcome among DSM IV depressive disorders with atypical features? *Neuropsychopharmacology*. 2002 Feb;26(2):237-45.
217. Stiebel VG. Maintenance electroconvulsive therapy for chronic mentally ill patients: a case series. *Psychiatr Serv*. 1995 Mar;46(3):265-8.
218. Stoudemire A, Hill CD, Morris R, Martino-Saltzman D, Lewison B. Long-term affective and cognitive outcome in depressed older adults. *Am J Psychiatry*. 1993 Jun;150(6):896-900.
219. Swartz CM, Morrow V, Surles L, James JF. Long-term outcome after ECT for catatonic depression. *J Ect*. 2001 Sep;17(3):180-3.
220. Swoboda E, Conca A, Konig P, Waanders R, Hansen M. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. *Neuropsychobiology*. 2001 Jan;43(1):23-8.
221. Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam JD, Gettes DR, et al. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biol Psychiatry*. 2001 Jul 1;50(1):22-7.
222. Taylor MP, Reynolds Iii CE, Frank E, Cornes C, Miller MD, Stack JA, et al. Which elderly depressed patients remain well on maintenance interpersonal psychotherapy alone?: Report from the Pittsburgh Study of Maintenance Therapies in late-life depression. *Depression and Anxiety*. 1999;10(2):55-60.
223. Tew JD, Jr., Mulsant BH, Houck PR, Lenze EJ, Whyte EM, Miller MD, et al. Impact of prior treatment exposure on response to antidepressant treatment in late life. *Am J Geriatr Psychiatry*. 2006 Nov;14(11):957-65.

224. Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry*. 2002 Mar;59(3):233-9.
225. Thase ME, Shelton RC, Khan A. Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. *J Clin Psychopharmacol*. 2006 Jun;26(3):250-8.
226. Thomas SA, Lincoln NB. Factors relating to depression after stroke. *British Journal of Clinical Psychology*. 2006;45(1):49-61.
227. Thompson C, Thompson CM. Treatment resistant or irresolutely treated? *Int Clin Psychopharmacol*. 1991 Jul;6 Suppl 1:31-8; discussion 8-9.
228. Thompson LW, Gallagher D, Breckenridge JS. Comparative effectiveness of psychotherapies for depressed elders. *Journal of Consulting and Clinical Psychology*. 1987;55(3):385-90.
229. Tielkes CE, Comijs HC, Verwijk E, Stek ML. The effects of ECT on cognitive functioning in the elderly: a review. *Int J Geriatr Psychiatry*. 2008 Aug;23(8):789-95.
230. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006 Mar 23;354(12):1243-52.
231. Tsourtos G, Spong J, Stough C. The effects of electro-convulsive therapy on the speed of information processing in major depression. *J Affect Disord*. 2007 Nov;103(1-3):263-6.
232. van den Broek WW, Birkenhager TK, Mulder PG, Bruijn JA, Moleman P. Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2006 Feb;67(2):263-8.
233. Van Der Starre PJA, Lemmens HJM, Chandel A, Solvason HB, Brock-Utne JG. The effects of esmolol and labetalol on cerebral blood flow velocity during electroconvulsive therapy [6]. *European Journal of Anaesthesiology*. 2008;25(2):174-6.
234. Van Der Wurff FB, Stek ML, Hoogendijk WJ, Beekman AT. The efficacy and safety of ECT in depressed older adults: a literature review (Brief record). *International Journal of Geriatric Psychiatry*. 2003(10):894-904.
235. Van Schaik A, Van Marwijk H, Adèr H, Van Dyck R, De Haan M, Penninx B, et al. Interpersonal psychotherapy for elderly patients in primary care. *American Journal of Geriatric Psychiatry*. 2006;14(9):777-86.
236. Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'Haenen H. A single session of rTMS over the left dorsolateral prefrontal cortex influences attentional control in depressed patients. *World J Biol Psychiatry*. 2009;10(1):34-42.
237. Vothknecht S, Kho KH, van Schaick HW, Zwinderman AH, Middelkoop H, Blansjaar BA. Effects of maintenance electroconvulsive therapy on cognitive functions. *J Ect*. 2003 Sep;19(3):151-7.
238. Wesson ML, Wilkinson AM, Anderson DN, Cracken CM. Does age predict the long-term outcome of depression treated with ECT? (a prospective study of the long-term outcome of ECT-treated depression with respect to age). *Int J Geriatr Psychiatry*. 1997 Jan;12(1):45-51.
239. White K, Wykoff W, Tynes LL, Schneider L, Zemansky M. Fluvoxamine in the treatment of tricyclic-resistant depression. *Psychiatr J Univ Ott*. 1990 Sep;15(3):156-8.
240. Wijkstra J, Burger H, van den Broek WW, Birkenhager TK, Janzing JG, Boks MP, et al. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. *Acta Psychiatr Scand*. 2009/08/22 ed 2010:190-200.
241. Wijkstra J, Lijmer J, Balk F, Geddes J, Nolen Willem A. Pharmacological treatment for psychotic depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd 2005.

242. Williams N, Simpson AN, Simpson K, Nahas Z. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Hum Psychopharmacol*. 2009/06/16 ed 2009:401-8.
243. Wilson K, Mottram PG, Vassilas C. Psychotherapeutic treatments for older depressed people. *Cochrane Database of Systematic Reviews*. 2008(1).
244. Winokur G, Coryell W, Keller M, Scheftner WA. Relationship of electroconvulsive therapy to course in affective illness: a collaborative study. *Eur Arch Psychiatry Clin Neurosci*. 1990;240(1):54-9.
245. Zapletal M, Zbytovsky J, Kudrnova K. Clinical experience with maprotilin and maprotilin/clomipramine infusions in resistant depression. *Acta Nerv Super (Praha)*. 1982 May;24(2):73-6.
246. Ziemann U, Ilia TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *Journal of Neuroscience*. 2004 Feb 2004;24(7):1666-72.
247. Zisook S, Rush AJ, Haight BR, Clines DC, Rockett CB. Use of bupropion in combination with serotonin reuptake inhibitors. *Biol Psychiatry*. 2006 Feb 1;59(3):203-10.
248. Zusky PM, Biederman J, Rosenbaum JF, Manschreck TC, Gross CC, Weilberg JB, et al. Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. *J Clin Psychopharmacol*. 1988 Apr;8(2):120-4.
249. Zvara DA, Brooker RF, McCall WV, Foreman AS, Hewitt C, Murphy BA, et al. The effect of esmolol on ST-segment depression and arrhythmias after electroconvulsive therapy. *Convuls Ther*. 1997 Sep;13(3):165-74.

Wrong Publication Type

1. Vagus nerve stimulation for treatment-resistance depression. *Technol Eval Cent Asses Program Exec Summ*. 2005 Aug;20(8):1-2.
2. Transcranial magnetic stimulation for depression. *Technol Eval Cent Asses Program Exec Summ*. 2009 Oct;24(5):1-3.
3. Easing the burden of treatment-resistant depression. *J Clin Psychiatry*. 2009 Feb;70(2):273-80.
4. Options for treatment-resistant depression. Why electroconvulsive therapy may be the best alternative to medication. *Harv Ment Health Lett*. 2009 Jan;25(7):1-3.
5. Transcranial magnetic stimulation. Research helps clarify who is likely to benefit from this treatment. *Harv Ment Health Lett*. 2010 Sep;27(3):6.
6. Abramowitz MZ, Lichtenberg P, Marcus E-L, Shapira B. Treating a Holocaust survivor without addressing the Holocaust: a case report. *Clinical Gerontologist*. 1994 1994;14(3):75-80.
7. Abrams R. Is unilateral electroconvulsive therapy really the treatment of choice in endogenous depression? *Ann N Y Acad Sci*. 1986;462:50-5.
8. American Psychiatric Association. Committee on Electroconvulsive T, Weiner RD. The practice of electroconvulsive therapy : a task force report of the American Psychiatric Association. Washington, D.C.: American Psychiatric Association.
9. Asaknow JR, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry*. 2009;48(3):330-9.
10. Ashton AK. Depressive relapse after vagal nerve stimulator explantation. *Am J Psychiatry*. 2010 Jun;167(6):719-20.
11. Avery D. Transcranial magnetic stimulation in the treatment of depression. *Essent Psychopharmacol*. 2001;4:37-48.

12. Bachar E, Lerer B, Shapira B. Increment in reminiscing after ECT: possible connections to neuropsychologic changes [2]. *J ECT*. 1999;15(2):165-6.
13. Barker AT, Jalinous R, Freeston H, Jarratt JA. Motor responses to noninvasive brain stimulation in clinical practice. *Electroencephalogr Clin Neurophysiol*. 1985;61:570-4.
14. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet*. 1985;1(8437):1106-7.
15. Bauer M, Adli M, Bschor T, Pilhatsch M, Pfennig A, Sasse J, et al. Lithium's emerging role in the treatment of refractory major depressive episodes: augmentation of antidepressants. *Neuropsychobiology*. 2010/05/11 ed 2010:36-42.
16. Bech P, Stokes PE, Greden JF, Tollefson GD. Acute therapy of depression. *Journal of Clinical Psychiatry*. 1993;54(8 SUPPL):18-27.
17. Bobo WV, Shelton RC. Fluoxetine and olanzapine combination therapy in treatment-resistant major depression: review of efficacy and safety data. *Expert Opin Pharmacother*. 2009 Sep;10(13):2145-59.
18. Bobo WV, Shelton RC. Efficacy, safety and tolerability of Symbyax for acute-phase management of treatment-resistant depression. *Expert Rev Neurother*. 2010 May;10(5):651-70.
19. Borckardt JJ, Anderson B, Kozel FA, Nahas Z, Smith AR, Thomas KJ, et al. Acute and long-term VNS effects on pain perception in a case of treatment-resistant depression. *Neurocase*. 2006 Aug 2006;12(4):216-20.
20. Chaput Y, Magnan A, Gendron A. The co-administration of quetiapine or placebo to cognitive-behavior therapy in treatment refractory depression: a preliminary trial. *BMC Psychiatry*. 2008;8:73.
21. Cheema FA, Badr A, Iqbal J. Glioblastoma multiforme presenting as treatment-resistant depression. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2010 Winter;22(1):E26.
22. Christmas David MB, Crombie I, Eljamel S, Fineberg N, MacVicar B, Matthews K, et al. Neurosurgery for obsessive-compulsive disorder, other anxiety disorders and depressive disorders. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd 2005.
23. Conca A, König P, Hausmann A. Transcranial magnetic stimulation induces 'pseudoabsence seizure'. *Acta Psychiatrica Scandinavica*. 2000 Mar 2000;101(3):246-8.
24. Coryell W, Tsuang MT. Primary unipolar depression and the prognostic importance of delusions. *Arch Gen Psychiatry*. 1982 Oct;39(10):1181-4.
25. Crow TJ, Johnstone EC. Controlled trials of electroconvulsive therapy. *Ann N Y Acad Sci*. 1986;462:12-29.
26. Croxtall JD, Scott LJ. Olanzapine/fluoxetine: a review of its use in patients with treatment-resistant major depressive disorder. *CNS Drugs*. 2010 Mar 1;24(3):245-62.
27. Culpepper L. Why do you need to move beyond first-line therapy for major depression? *J Clin Psychiatry*. 2010/11/05 ed 2010:4-9.
28. Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. *Psychopharmacol Bull*. 2009/07/25 ed 2009:5-38.
29. Dinan TG. A rational approach to the non-responding depressed patient. *International Clinical Psychopharmacology*. 1993;8(4):221-3.
30. Dunner DL, Russell JM. A long-term, naturalistic study of usual standard-of-care treatment in patients with treatment resistant depression. Proceedings of the ACNP Annual Meeting, San Juan, Puerto Rico, December 2003. 2003:150.
31. Ella R, Zwanzger P, Stampfer R, Preuss UW, Müller-Siecheneder F, Möller H-J, et al. Switch to mania after slow rTMS of the right prefrontal cortex. *Journal of Clinical Psychiatry*. 2002 Mar 2002;63(3):249.
32. Fava M. The combination of buspirone and bupropion in the treatment of depression. *Psychother Psychosom*. 2007;76(5):311-2.

33. Fink M. *Electroshock: restoring the mind*. New York: Oxford University Press 1999.
34. Fink M. Electroconvulsive therapy in medication-resistant depression. *Treatment-Resistant Mood Disorders*. 2001:223-38.
35. Floyd MR. Cognitive therapy for depression: a comparison of individual psychotherapy and bibliotherapy for depressed older adults. Dissertation Abstracts International. 1999;58(9 -B):5081.
36. Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M. The STAR*D study: treating depression in the real world. *Cleve Clin J Med*. 2008 Jan;75(1):57-66.
37. Geddes J, Butler R. Depressive disorders. *Clin Evid*. 2002 Jun(7):867-82.
38. George MS, Belmaker RH. *Transcranial magnetic stimulation in neuropsychiatry*. Washington, DC: American Psychiatric Press 2000.
39. George MS, Sackeim HA, Marangell LB, Husain MM, Nahas Z, Lisanby SH, et al. Vagus nerve stimulation: A potential therapy for resistant depression? *Psychiatric Clinics of North America*. 2000 Dec 2000;23(4):757-83.
40. George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation and ECT. *Convulsive Therapy*. 1994;10(4):251-4; discussion 5.
41. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry*. 2003 May;160(5):835-45.
42. Goff DC, Jenike MA. Treatment-resistant depression in the elderly. *J Am Geriatr Soc*. 1986 Jan;34(1):63-70.
43. Goforth HW, Carroll BT. Aripiprazole augmentation of tranylcypromine in treatment-resistant major depression [8]. *Journal of Clinical Psychopharmacology*. 2007 Apr;27 (2):216-7.
44. Goodnick PJ, Barrios CA. Use of olanzapine in non-psychotic psychiatric disorders. *Expert Opinion on Pharmacotherapy*. 2001;2(4):667-80.
45. Gormley N. ECT should be treatment option in all cases of refractory depression [7]. *British Medical Journal* 1998;316(7126):233.
46. Grisaru N, Yaroslavsky U, Abarbanel J, Lamberg T, Belmaker RH. Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology*. 1994;4(3):287-8.
47. Grunhaus L, Remen A. Assessment of treatment-resistant major depression - The Michigan adequacy of treatment scale [4]. *Journal of Clinical Psychopharmacology*. 1993;13(3):221-3.
48. Guthrie SK, Sung JCY, Goodson J, Grunhaus L, Tandon R. Triazolam and diphenhydramine effects on seizure duration in depressed patients receiving ECT. *Convulsive Therapy*. 1996;12(4):261-5.
49. Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M, et al. Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. *Journal of Psychiatric Research*. 2003 Jul-Aug 2003;37(4):267-75.
50. Höflich G, Kasper S, Hufnagel A, Ruhrmann S, Möller H-J. Application of transcranial magnetic stimulation in treatment of drug-resistant major depression: A report of two cases. *Human Psychopharmacology: Clinical and Experimental*. 1993 Sep-Oct 1993;8(5):361-5.
51. Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller HJ. Application of transcranial magnetic stimulation in treatment of drug-resistant major depression - A report of two cases. *Human Psychopharmacology*. 1993;8(5):361-5.
52. Holtzheimer PE, Avery D, Schlaepfer TE. Antidepressant effects of repetitive transcranial magnetic stimulation [4]. *British Journal of Psychiatry*. 2004;184(JUNE):541-2.
53. Howland RH. Chronic depression. *Hospital and Community Psychiatry*. 1993;44(7):633-9.

54. Huang CC, Su TP, Shan IK, Chang K, Wei IH. An open trial of daily left prefrontal cortex repetitive transcranial magnetic stimulation for treating medication-resistant depression. *Eur Psychiatry*. 2004 Dec;19(8):523-4.
55. Iosifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. *Current Psychiatry Reports*. 2004;6(3):193-201.
56. Johnson BA, Cowen PJ. Calcium channel blockade and resistant bipolar depression. *Irish Journal of Psychological Medicine*. 1991 Mar 1991;8(1):50-1.
57. Jorge RE, Robinson RG, O'Brien J. Top cited papers in international psychogeriatrics: 5. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr*. 2009 Oct;21(5):855-60.
58. Kaplan B, Chistyakov A, Kreinin I, Hafner H, Feinsod M, Klein E. The effect of electro-convulsive therapy and repetitive transcranial magnetic stimulation on cortical excitability in patients with major depression. *Muscle & Nerve Supplement*. 2003;12.
59. Kellner CH, Husain M, Petrides G, Fink M, Rummans T. Comment on "Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial". *Biol Psychiatry*. 2002 Nov 15;52(10):1032-3; discussion 3.
60. Kellner M. Aripiprazole in a therapy-resistant patient with borderline personality and post-traumatic stress disorder. *Pharmacopsychiatry*. 2007 Jan 2007;40(1):41.
61. Kiloh LG. Non-pharmacological biological treatments of psychiatric patients. *Aust N Z J Psychiatry*. 1983 Sep;17(3):215-25.
62. Kimball JN, Rosenquist PB, Dunn A, McCall V. Prediction of antidepressant response in both 2.25xthreshold RUL and fixed high dose RUL ECT. *J Affect Disord*. 2009 Jan;112(1-3):85-91.
63. Kojima H, Terao T, Yoshimura R. Serotonin syndrome during clomipramine and lithium treatment [1]. *American Journal of Psychiatry*. 1993;150(12).
64. Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depression and Anxiety*. 2004 2004;20(2):98-100.
65. Loo CK, Kaill A, Paton P, Simpson B. The difficult-to-treat electroconvulsive therapy patient - Strategies for augmenting outcomes. *Journal of affective disorders*. 2010 August;124 (3):219-27.
66. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol*. 2008 Feb;11(1):131-47.
67. Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *J Affect Disord*. 2005 Nov;88(3):255-67.
68. McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine*. 2001;31(7):1141-6.
69. Milev R, Abraham G, Hasey G, Cabaj JL. Repetitive transcranial magnetic stimulation for treatment of medication-resistant depression in older adults: a case series. *J Ect*. 2009 Mar;25(1):44-9.
70. Morgan PT. Treatment-resistant depression: Response to low-dose transdermal but not oral selegiline [10]. *Journal of Clinical Psychopharmacology*. 2007 Jun;27 (3):313-4.
71. Moustgaard G. Treatment-refractory depression successfully treated with the combination of mirtazapine and lithium. *J Clin Psychopharmacol* 2000:268.
72. Mulrow CD, Williams JW, Jr., Trivedi M, Chiquette E, Aguilar C, Cornell JE, et al. Treatment of depression--newer pharmacotherapies. *Psychopharmacol Bull*. 1998;34(4):409-795.
73. Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. *Psychiatr Clin North Am*. 2007 Mar;30(1):13-29.

74. Nolen WA, Van Den Broek WW, Birkenhager TK. Treatment with low doses of tranylcypromine resulted in a disappointing remission rate [1]. *American Journal of Psychiatry* 2007;164(3):524.
75. Okamoto H, Shimizu E, Ozawa K, Hashimoto K, Iyo M. Lithium augmentation in milnacipran-refractory depression for the prevention of relapse following electroconvulsive therapy [1]. *Australian and New Zealand Journal of Psychiatry*. 2005 Jan;39 (1-2):108.
76. Okay T, Sengul C, Gulunay A, Sengul CB, Erken DD, Dilbaz N. The short term effects of naproxen sodium on treatment satisfaction and headache as a side-effect of electroconvulsive therapy: A preliminary study. *Klinik Psikofarmakoloji Bulteni*. 2008;18(1):41-5.
77. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology*. 1998;15(4):333-43.
78. Poirier MF. [The concept of resistant depression and therapeutic strategies, particularly, with venlafaxine]. *Encephale*. 1999 Jun;25 Spec No 2:55-7; discussion 8-61.
79. Rasmussen KG. Electroconvulsive therapy versus transcranial magnetic stimulation for major depression: A review with recommendations for future research. *Acta Neuropsychiatrica*. 2008;20(6):291-4.
80. Rosenberg O, Shoenfeld N, Kotler M, Dannon PN. Mood disorders in elderly population: Neurostimulative treatment possibilities. *Recent Patents on CNS Drug Discovery*. 2009;4(2):149-55.
81. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. *J Clin Psychiatry*. 1998;59 Suppl 5:32-9; discussion 40-1.
82. Rush AJ, Gullion CM, Roffwarg HP. When do patients respond to tricyclic antidepressants? *Biol Psychiatry*. 1994;35:711-7.
83. Rush AJ, Kilner J, Fava M, Wisniewski SR, Warden D, Nierenberg AA, et al. Clinically relevant findings from STAR*D. *Psychiatric Annals*. 2008 03;38(3):188-93.
84. Sackeim HA. Magnetic stimulation therapy and ECT. *Convuls Ther*. 1994;10(4):255-8.
85. Sackeim HA. Repetitive transcranial magnetic stimulation: What are the next steps? *Biological Psychiatry*. 2000;48(10):959-61.
86. Sackeim HA. Memory and ECT: from polarization to reconciliation. *J ECT*. 2000;16(2):87-96.
87. Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A, et al. Induction of mania by rTMS: report of two cases. *European Psychiatry*. 2003 Jun 2003;18(4):196-8.
88. Samaras N, Rossi G, Giannakopoulos P, Gold G. Vascular depression. An age-related mood disorder. *European Geriatric Medicine*. 2010;1 (4):220-5.
89. Santos MA, Hara C, Stumpf BLP, Rocha FL. Treatment-resistant depression: Review of pharmacologic antidepressant strategies. *Jornal Brasileiro de Psiquiatria*. 2006;55(3):232-42.
90. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry*. 1989 Jul;50(7):241-9.
91. Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. *NeuroRx*. 2005 Oct;2(4):590-611.
92. Schopf J. Treatment of depressions resistant to tricyclic antidepressants, related drugs or MAO-inhibitors by lithium addition: review of the literature. *Pharmacopsychiatry*. 1989 Sep;22(5):174-82.
93. Schramm E, Schneider D, Zobel I, van Calker D, Dykieriek P, Kech S, et al. Efficacy of interpersonal psychotherapy plus pharmacotherapy in chronically depressed inpatients. *Journal of Affective Disorders*. 2008 Jul 2008;109(1):65-73.

94. Schweitzer I, Tuckwell V, Johnson G. A review of the use of augmentation therapy for the treatment of resistant depression: implications for the clinician. *Aust N Z J Psychiatry*. 1997 Jun;31(3):340-52.
95. Scott J. Treatment of chronic depression. *New England Journal of Medicine*. 2000;342(20):1518-20.
96. Shelton RC. Mood-stabilizing drugs in depression. *J Clin Psychiatry*. 1999;60 Suppl 5:37-40; discussion 1-2.
97. Shelton RC. Treatment options for refractory depression. *J Clin Psychiatry*. 1999;60 Suppl 4:57-61; discussion 2-3.
98. Shelton RC, Papakostas GI. Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder. *Acta Psychiatr Scand*. 2008 Apr;117(4):253-9.
99. Shuchman M. Approving the vagus-nerve stimulator for depression. *New England Journal of Medicine*. 2007;356(16):1604-7.
100. Small JG, Small IF. Electroconvulsive therapy update. *Psychopharmacol Bull*. 1981 Oct;17(4):29-42.
101. Sonawalla SB, Fava M. Severe depression: is there a best approach? *CNS Drugs*. 2001;15(10):765-76.
102. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol*. 1999 Jan;9(1-2):83-91.
103. Souery D, Van der Auwera K. The multiple facets of treatment-resistant depression. *CNS Spectr*. 2004 Nov;9(11):803-7.
104. Spitzer RL, National Institute of Mental Health (U.S.). *User's guide for the structured clinical interview for DSM-III-R: SCID*. Washington, DC: American Psychiatric Press 1990.
105. St John D. Pharmacotherapeutic approaches to treatment-resistant depression. *Jaapa*. 2003 Mar;16(3):32-4, 7-8, 40 passim.
106. Standish-Barry H. Treating refractory depression. *Int Clin Psychopharmacol*. 1990 Jul;5 Suppl 3:33-43.
107. Stern SL, Mendels J. Drug combinations in the treatment of refractory depression: a review. *J Clin Psychiatry*. 1981 Oct;42(10):368-73.
108. Tanum LH. Combination treatment with antidepressants in refractory depression. *Int Clin Psychopharmacol*. 1994 Jun;9 Suppl 2:37-40.
109. Taylor D. Selective serotonin reuptake inhibitors and tricyclic antidepressants in combination. Interactions and therapeutic uses. *Br J Psychiatry*. 1995 Nov;167(5):575-80.
110. Thase Jr ME, Rush Jr AJ. Treatment-resistant depression. *Treatment-Resistant Depression in Psychopharmacology: The Fourth Generation of Progress*. 1995.
111. Thase ME. The need for clinically relevant research on treatment-resistant depression. *J Clin Psychiatry*. 2001 Apr;62(4):221-4.
112. Thase ME. Pharmacologic and therapeutic strategies in treatment-resistant depression. Augmentation strategies. *CNS Spectr*. 2009 Mar;14(3 Suppl 4):7-10.
113. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58 Suppl 13:23-9.
114. Thomas SA, Lincoln NB. Factors relating to depression after stroke. *Clinical Rehabilitation*. 2004;18(5):589-90.
115. Tierney JG. Treatment-resistant depression: managed care considerations. *J Manag Care Pharm*. 2007 Jul;13(6 Suppl A):S2-7.
116. Tobin M. Psychopharmacology column: why choose selegiline transdermal system for refractory depression? *Issues Ment Health Nurs*. 2007 Feb;28(2):223-8.
117. Tremblay P, Blier P. Catecholaminergic strategies for the treatment of major depression. *Curr Drug Targets*. 2006 Feb;7(2):149-58.
118. Triezenberg D, Vachon D, Helmen J, Schneider D. Clinical inquiries: How should you manage a depressed patient unresponsive to an SSRI? *J Fam Pract*. 2006 Dec;55(12):1081-2, 7.
119. Trimble MR. Worldwide use of clomipramine. *J Clin Psychiatry*. 1990 Aug;51 Suppl:51-4; discussion 5-8.

120. Trivedi MH. Treatment-resistant depression: new therapies on the horizon. *Ann Clin Psychiatry*. 2003 Mar;15(1):59-70.
121. Trivedi MH, Daly EJ. Treatment strategies to improve and sustain remission in major depressive disorder. *Dialogues Clin Neurosci*. 2008;10(4):377-84.
122. Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. *CNS Spectr*. 2007 Aug;12(8 Suppl 13):1-27.
123. Unutzer J. Late-life depression. *New England Journal of Medicine*. 2007;357(22):2269-76.
124. Vanderhasselt MA, De Raedt R, Leyman L, Baeken C. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. *J Psychiatry Neurosci*. 2009 Mar;34(2):119-26.
125. Wager SG, Klein DF. Drug therapy strategies for treatment-resistant depression. *Psychopharmacol Bull*. 1988;24(1):69-74.
126. Warneke L. Managing resistant depression. When patients do not respond to therapy. *Can Fam Physician*. 1993 Apr;39:843-50.
127. Warneke L. Management of resistant depression. *Can Fam Physician*. 1996 Oct;42:1973-80.
128. Wells KB, Sturm R, Sherbourne CD, Meredith LS. Caring for Depression. *Caring for Depression*. 1996.
129. Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. *Aust N Z J Psychiatry*. 2008 Sep;42(9):751-62.
130. Wilhelm K, Mitchell P, Boyce P, Hickie I, Brodaty H, Austin MP, et al. Treatment resistant depression in an Australian context. I: The utility of the term and approaches to management. *Aust N Z J Psychiatry*. 1994 Mar;28(1):14-22.
131. Williams GO. Management of depression in the elderly. *Prim Care*. 1989 Jun;16(2):451-74.
132. Woggon B. Methodology of measuring the efficacy of antidepressants--European viewpoint. *Psychopharmacology (Berl)*. 1992;106 Suppl:S90-2.
133. Yip AG, Carpenter LL. Transcranial magnetic stimulation for medication-resistant depression. *J Clin Psychiatry*. 2010 Apr;71(4):502-3.
134. Young SN. Use of tryptophan in combination with other antidepressant treatments: a review. *J Psychiatry Neurosci*. 1991 Dec;16(5):241-6.
135. Zetin M, Hoepner CT, Bjornson L. Rational antidepressant selection: applying evidence-based medicine to complex real-world patients. *Psychopharmacol Bull*. 2006;39(1):38-104.
136. Zhang X, Liu K, Sun J, Zheng Z. Safety and feasibility of repetitive transcranial magnetic stimulation (rTMS) as a treatment for major depression during pregnancy. *Arch Womens Ment Health*. 2010 Aug;13(4):369-70.
137. Zullino D, Baumann P. Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. *Pharmacopsychiatry*. 2001 Jul;34(4):119-27.

Wrong Outcome

1. Agelink MW, Andrich J, Postert T, Wurzinger U, Zeit T, Klotz P, et al. Relation between electroconvulsive therapy, cognitive side effects, neuron specific enolase, and protein S-100. *J Neurol Neurosurg Psychiatry*. 2001 Sep;71(3):394-6.
2. Amiaz R, Stein O, Schreiber S, Danon PN, Dolberg OT, Grunhaus L. Magnetic and seizure thresholds before and after six electroconvulsive treatments. *J Ect*. 2001 Sep;17(3):195-7.

3. Babigian HM, Guttmacher LB. Epidemiologic considerations in electroconvulsive therapy. *Arch Gen Psychiatry*. 1984 Mar;41(3):246-53.
4. Baeken C, De Raedt R, Leyman L, Schiettecatte J, Kaufman L, Poppe K, et al. The impact of one HF-rTMS session on mood and salivary cortisol in treatment resistant unipolar melancholic depressed patients. *J Affect Disord*. 2009 Feb;113(1-2):100-8.
5. Baeken C, De Raedt R, Vanderhasselt MA, Leyman L, Schiettecatte J, Poppe K, et al. A "hypersensitive" hypothalamic-pituitary-adrenal system could be indicative for a negative clinical high-frequency repetitive transcranial magnetic stimulation outcome in melancholic depressed patients. *Brain Stimulation* 2010:54-7.
6. Bajbouj M, Gallinat J, Lang UE, Neu P, Niehaus L. Motorcortical excitability after electroconvulsive therapy in patients with major depressive disorder. *Suppl Clin Neurophysiol*. 2003;56:433-40.
7. Bauer M, Bschor T, Kunz D, Berghofer A, Strohle A, Muller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *The American Journal of Psychiatry*. 2000 09;157(9):1429-35.
8. Bosworth HB, McQuoid DR, George LK, Steffens DC. Time-to-remission from geriatric depression: psychosocial and clinical factors. *Am J Geriatr Psychiatry*. 2002 Sep-Oct;10(5):551-9.
9. Carpenter LL, Moreno FA, Kling MA, Anderson GM, Regenold WT, Labiner DM, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biological Psychiatry*. 2004 Sep 2004;56(6):418-26.
10. Chae JH, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *Journal of Psychiatric Research*. 2003;37(6):443-55.
11. Coffey CE, Weiner RD, Djang WT, Figiel GS, Soady SA, Patterson LJ, et al. Brain anatomic effects of electroconvulsive therapy. A prospective magnetic resonance imaging study. *Arch Gen Psychiatry*. 1991 Nov;48(11):1013-21.
12. Conca A, Peschina W, König P, Fritzsche H, Hausmann A. Effect of chronic repetitive transcranial magnetic stimulation on regional cerebral blood flow and regional cerebral glucose uptake in drug treatment-resistant depressives: A brief report. *Neuropsychobiology*. 2002 Jan 2002;45(1):27-31.
13. Dang T, Avery DH, Russo J. Within-session mood changes from TMS in depressed patients. *J Neuropsychiatry Clin Neurosci*. 2007 Fall;19(4):458-63.
14. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L. Magnetic motor threshold and response to TMS in major depressive disorder. *Acta Psychiatrica Scandinavica*. 2002 Sep 2002;106(3):220-3.
15. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry*. 2006 May;67(5):688-95.
16. Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, et al. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Research: Neuroimaging*. 2000 Oct 2000;99(3):161-72.
17. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*. 2009 Apr;34(5):1255-62.
18. Greenhalgh J, Knight C, Hind D, Beverley C, Walters S. Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies. *Health Technol Assess*. 2005 Mar;9(9):1-156, iii-iv.

19. Grunhaus L, Hirschman S, Dolberg OT, Schreiber S, Dannon PN. Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. *J Ect*. 2001 Jun;17(2):124-8.
20. Grunhaus L, Shipley JE, Eiser A, Pande AC, Tandon R, Remen A, et al. Shortened REM latency PostECT is associated with rapid recurrence of depressive symptomatology. *Biol Psychiatry*. 1994 Aug 15;36(4):214-22.
21. Grunhaus L, Shipley JE, Eiser A, Pande AC, Tandon R, Remen A, et al. Polysomnographic studies in patients referred for ECT: pre-ECT studies. *Convuls Ther*. 1996 Dec;12(4):224-31.
22. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, et al. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. *Biol Psychiatry*. 2009/06/24 ed 2009:509-15.
23. Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry*. 2007 Nov;191:441-8.
24. Kelway B, Simpson KH, Smith RJ, Halsall PJ. Effects of atropine and glycopyrrolate on cognitive function following anaesthesia and electroconvulsive therapy (ECT). *Int Clin Psychopharmacol*. 1986 Oct;1(4):296-302.
25. Lang UE, Hellweg R, Gallinat J, Bajbouj M. Acute prefrontal cortex transcranial magnetic stimulation in healthy volunteers: no effects on brain-derived neurotrophic factor (BDNF) concentrations in serum. *J Affect Disord*. 2008 Apr;107(1-3):255-8.
26. Lenox RH, Peyser JM, Rothschild B, Shipley J, Weaver L. Failure to normalize the dexamethasone suppression test: association with length of illness. *Biol Psychiatry*. 1985 Mar;20(3):333-7.
27. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009 Jan;34(2):522-34.
28. Luber B, Nobler MS, Moeller JR, Katzman GP, Prudic J, Devanand DP, et al. Quantitative EEG during seizures induced by electroconvulsive therapy: relations to treatment modality and clinical features. II. Topographic analyses. *J Ect*. 2000 Sep;16(3):229-43.
29. Munk-Olsen T, Laursen TM, Videbech P, Mortensen PB, Rosenberg R. All-cause mortality among recipients of electroconvulsive therapy: Register-based cohort study. *British Journal of Psychiatry*. 2007;190(MAY):435-9.
30. Murthy PJ, Gangadhar BN, Janakiramaiah N, Subbakrishna DK. Normalization of P300 amplitude following treatment in dysthymia. *Biol Psychiatry*. 1997 Oct 15;42(8):740-3.
31. Nahas Z, Teneback C, Chae JH, Mu Q, Molnar C, Kozel FA, et al. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology*. 2007 Aug;32(8):1649-60.
32. Navarro R, Zarkowski P, Sporn A, Avery D. Hemispheric asymmetry in resting motor threshold in major depression. *J Ect*. 2009 Mar;25(1):39-43.
33. Nelson AL, Cohen JT, Greenberg D, Kent DM. Much cheaper, almost as good: decrementally cost-effective medical innovation. *Ann Intern Med*. 2009/11/04 ed 2009:662-7.
34. O'Connor KP, Colter N, Shaw JC. Cognitive style, cortical function, and electroconvulsive therapy. *J Nerv Ment Dis*. 1984 Dec;172(12):711-7.
35. Pande AC, Grunhaus LJ, Aisen AM, Haskett RF. A preliminary magnetic resonance imaging study of ECT-treated depressed patients. *Biol Psychiatry*. 1990 Jan 1;27(1):102-4.

36. Papakostas YG, Markianos M, Zervas IM, Theodoropoulou M, Vaidakis N, Daras M. Administration of citalopram before ECT: seizure duration and hormone responses. *J Ect*. 2000 Dec;16(4):356-60.
37. Prudic J, Fitzsimons L, Nobler MS, Sackeim HA. Naloxone in the prevention of the adverse cognitive effects of ECT: a within-subject, placebo controlled study. *Neuropsychopharmacology*. 1999 Aug;21(2):285-93.
38. Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. *Neuropsychopharmacology*. 2006/06/09 ed 2006:2505-13.
39. Rasmussen KG, Mueller M, Rummans TA, Husain MM, Petrides G, Knapp RG, et al. Is baseline medication resistance associated with potential for relapse after successful remission of a depressive episode with ECT? Data from the Consortium for Research on Electroconvulsive Therapy (CORE). *J Clin Psychiatry*. 2009 Feb;70(2):232-7.
40. Rasmussen KG, Stevens SR, Kung S, Mohan A. Melancholic symptoms as assessed by the Hamilton Depression Rating Scale and outcomes with and without electroconvulsive therapy on an in-patient mood disorders unit. *Acta Neuropsychiatrica*. 2010;22(1):21-5.
41. Recart A, Rawal S, White PF, Byerly S, Thornton L. The effect of remifentanyl on seizure duration and acute hemodynamic responses to electroconvulsive therapy. *Anesth Analg*. 2003 Apr;96(4):1047-50, table of contents.
42. Rohland BM. Self-report of improvement following hospitalization for electroconvulsive therapy: relationship to functional status and service use. *Adm Policy Ment Health*. 2001 Jan;28(3):193-203.
43. Saravanan ES, Gangadhar BN, Janakiramaiah N, Pandey RS, Murthy HS, Subbakrishna DK. Does higher cardiovascular response to ECT predict early antidepressant effect? *J Affect Disord*. 2002 May;69(1-3):101-8.
44. Sawayama E, Takahashi M, Inoue A, Nakajima K, Kano A, Sawayama T, et al. Moderate hyperventilation prolongs electroencephalogram seizure duration of the first electroconvulsive therapy. *J Ect*. 2008 Sep;24(3):195-8.
45. Scott AI, Boddy H. The effect of repeated bilateral electroconvulsive therapy on seizure threshold. *J Ect*. 2000 Sep;16(3):244-51.
46. Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychol Med*. 1998 Sep;28(5):1015-26.
47. Stern RA, Nevels CT, Shelhorse ME, Prohaska ML, Mason GA, Prange AJ, Jr. Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: preliminary findings. *Biol Psychiatry*. 1991 Sep 15;30(6):623-7.
48. Swan J, Sorrell E, MacVicar B, Durham R, Matthews K. "Coping with depression": an open study of the efficacy of a group psychoeducational intervention in chronic, treatment-refractory depression. *J Affect Disord*. 2004 Oct 1;82(1):125-9.
49. Tang WK, Ungvari GS, Leung HC. Effect of piracetam on ECT-induced cognitive disturbances: a randomized, placebo-controlled, double-blind study. *J Ect*. 2002 Sep;18(3):130-7.
50. Van HL, Dekker J, Peen J, van Aalst G, Schoevers RA. Identifying patients at risk of complete nonresponse in the outpatient treatment of depression. *Psychother Psychosom*. 2008;77(6):358-64.
51. Wilkinson P, Hawton K, Andrew B, Fagg J. Does the duration of illness before treatment affect the time taken to recover on treatment in severely depressed women? *J Affect Disord*. 1996 Nov 25;41(2):89-92.

52. Yukimasa T, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda N, et al. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry*. 2006 Mar;39(2):52-9.
53. Zubenko GS, Mulsant BH, Rifai AH, Sweet RA, Pasternak RE, Marino LJ, Jr., et al. Impact of acute psychiatric inpatient treatment on major depression in late life and prediction of response. *Am J Psychiatry*. 1994 Jul;151(7):987-94.

Published Prior to 1980

1. Abrams R, DeVito RA. Clinical efficacy of unilateral ECT. *Diseases of the nervous system*. 1969;30(4):262-3.
2. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Archives of General Psychiatry*. 1976;33(9):1029-37.
3. Barton JL, Mehta S, Snaith RP. The prophylactic value of extra ECT in depressive illness. *Acta Psychiatrica Scandinavica*. 1973;49(4):386-92.
4. Bidder TG, Strain JJ, Brunschwig L. Bilateral and unilateral ECT: follow-up study and critique. *American Journal of Psychiatry*. 1970;127(6):737-45.
5. Bratfos O, Haug JO. Electroconvulsive therapy and antidepressant drugs in manic-depressive disease. Treatment results at discharge and 3 months later. *Acta Psychiatrica Scandinavica*. 1965;41(4):588-96.
6. Bruce EM, Crone N, Fitzpatrick G, Frewin SJ, Gillis A, Lascelles CF, et al. A comparative trial of ECT and tofranil. *American Journal of Psychiatry*. 1960;117:76.
7. Carney MW, Rogan PA, Sebastian J, Sheffield B. A controlled comparative trial of unilateral and bilateral sinusoidal and pulse E.C.T. in endogenous depression. *Physicians' Drug Manual*. 1976;7:9-128/1.
8. Costello CG, Belton GP, Abra JC, Dunn BE. The amnesic and therapeutic effects of bilateral and unilateral ECT. *British Journal of Psychiatry*. 1970;116(530):69-78.
9. Davidson J, McLeod M, Law-Yone B. A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. *Archives of General Psychiatry*. 1978;35(5):639-42.
10. D'Elia G. Comparison of electroconvulsive therapy with unilateral and bilateral stimulation, II: Therapeutic efficacy in endogenous depression. *Acta Psychiatr Scand*. 1970;215:30-43.
11. D'Elia G. Comparison of electroconvulsive therapy with unilateral and bilateral stimulation, III: Anterograde amnesia. *Acta Psychiatr Scand Suppl*. 1970;212:44-60.
12. Fleminger JJ, de Horne DJ, Nair NP, Nott PN. Differential effect of unilateral and bilateral ECT. *American Journal of Psychiatry*. 1970;127(4):430-6.
13. Freeman CPL, Basson JV, Crighton A. Double-blind controlled trial of electroconvulsive therapy (E.C.T.) and simulated E.C.T. in depressive illness. *Lancet*. 1978;1(8067):738-40.
14. Fromholt P, Christensen AL, Sand Stromgren L. The effects of unilateral and bilateral electroconvulsive therapy on memory. *Acta Psychiatrica Scandinavica*. 1973;49(4):466-78.
15. Halliday AM, Davison K, Browne MW, Kreeger LC. A comparison of the effects on depression and memory of bilateral E.C.T. and unilateral E.C.T. to the dominant and non-dominant hemispheres. *British Journal of Psychiatry*. 1968;114(513):997-1012.
16. Herrington RN, Bruce A, Johnstone EC, Lader MH. Comparative trial of L tryptophan and E.C.T. in severe depressive illness. *Lancet*. 1974;2(7883):731-4.
17. Heshe J, Röder E, Theilgaard A. Unilateral and bilateral ECT. A psychiatric and psychological study of therapeutic effect and side effects. *Acta Psychiatrica Scandinavica, Supplement*. 1978(275):1-180.

18. Hutchinson J, Smedberg D. Treatment of depression: A comparative study of ECT and six drugs. *Br J Psychiatry*. 1963;109:536-8.
19. Levy R. The clinical evaluation of unilateral electroconvulsive therapy. *British Journal of Psychiatry*. 1968;114(509):459-63.
20. Mandel MR, Welch CA, Mieske M. Prediction of response to ECT in tricyclic-intolerant or tricyclic-resistant depressed patients. *McLean Hosp J*. 1977;4:203-9.
21. McDonald IM, Perkins M, Marjerrison G, Podilsky M. A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. *American Journal of Psychiatry*. 1966;122(12):1427-31.
22. Robin A, Harris JA. A controlled comparison of imipramine and electroplexy. *J Ment Sci*. 1962;108:217-9.
23. Stanley W, Fleming H. A clinical comparison of phenelzine and electroconvulsive therapy in the treatment of depressive illness. *Br J Psychiatry*. 1962;108:708-10.
24. Steiner M, Radwan M, Elizur A. Failure of L-triiodothyronine (T3) to potentiate tricyclic antidepressant response. *Current Therapeutic Research - Clinical and Experimental*. 1978;23(5 II):655-9.
25. Strömgen LS. Unilateral versus bilateral electroconvulsive therapy. Investigations into the therapeutic effect in endogenous depression. *Acta Psychiatrica Scandinavica, Supplement*. 1973;240:8-65.
26. Thiery M. Clinical trial of the treatment of depressive illness. *BMJ*. 1965;1:881-6.
27. Wilson IC, Vernon JT, Guin T. A controlled study of treatments of depression. *J Neuropsychiatry*. 1963;4:331-7.

Wrong Intervention

1. Asnis GM, Halbreich U, Nathan RS, Ostrow L, Novacenko H, Endicott J, et al. The dexamethasone suppression test in depressive illness: clinical correlates. *Psychoneuroendocrinology*. 1982;7(4):295-301.
2. Bosworth HB, Hays JC, George LK, Steffens DC. Psychosocial and clinical predictors of unipolar depression outcome in older adults. *Int J Geriatr Psychiatry*. 2002 Mar;17(3):238-46.
3. Cassidy F, Weiner RD, Cooper TB, Carroll BJ. Combined catecholamine and indoleamine depletion following response to ECT. *British Journal of Psychiatry*. 2010 June;196(6):493-4.
4. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychopharmacol*. 2008 Aug;11(5):685-99.
5. Coppen A. Lithium in unipolar depression and the prevention of suicide. *J Clin Psychiatry*. 2000;61 Suppl 9:52-6.
6. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):641-54.
7. Huber R, MÃ¼ller S, Esser SK, Sarasso S, Ferrarelli F, Watson A, et al. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *Journal of Neuroscience*. 2008 Jul 2008;28(31):7911-8.
8. Kennedy N, Paykel ES. Treatment and response in refractory depression: results from a specialist affective disorders service. *J Affect Disord*. 2004 Jul;81(1):49-53.
9. Kirov G, Ebmeier KP, Scott AI, Atkins M, Khalid N, Carrick L, et al. Quick recovery of orientation after magnetic seizure therapy for major depressive disorder. *Br J Psychiatry*. 2008 Aug;193(2):152-5.

10. Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr Scand.* 1996 Oct;94(4):241-51.
11. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol Psychiatry.* 2004 May 1;55(9):882-90.
12. Mathew SJ, Murrrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial. *International Journal of Neuropsychopharmacology.* 2010;13(1):71-82.
13. Mayur PM, Gangadhar BN, Subbakrishna DK, Janakiramaiah N. Discontinuation of antidepressant drugs during electroconvulsive therapy: a controlled study. *J Affect Disord.* 2000 Apr;58(1):37-41.
14. Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy. *Journal of Anesthesia.* 2009;23(1):6-10.
15. Neuhaus AH, Gallinat J, Bajbouj M, Reischies FM. Interictal slow-wave focus in left medial temporal lobe during bilateral electroconvulsive therapy. *Neuropsychobiology.* 2005;52(4):183-9.
16. O'Reardon JP, Chopra MP, Bergan A, Gallop R, DeRubeis RJ, Crits-Christoph P. Response to tryptophan depletion in major depression treated with either cognitive therapy or selective serotonin reuptake inhibitor antidepressants. *Biol Psychiatry.* 2004 May 1;55(9):957-9.
17. Rocha FL, Hara C. Lamotrigine augmentation in unipolar depression. *Int Clin Psychopharmacol.* 2003 Mar;18(2):97-9.
18. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry.* 2006;163(11):1905-17.
19. Santos MA, Rocha FL, Hara C. Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: A randomized, placebo-controlled, double-blind study. *Primary Care Companion to the Journal of Clinical Psychiatry.* 2008;10(3):187-90.
20. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessaer D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology.* 2008 Jan 2008;33(2):368-77.
21. Shajahan PM, Glabus MF, Jenkins JA, Ebmeier KP. Postexercise motor evoked potentials in depressed and recovered depressed patients, and controls. *Neurology.* 1999 Aug 1999;53(3):644-6.
22. Shapira B, Oppenheim G, Zohar J, Segal M, Malach D, Belmaker RH. Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. *Biol Psychiatry.* 1985 May;20(5):576-9.
23. Small JG, Kellams JJ, Dennis JL, Milstein V. Comparison of molindone and tranlycypromine in the treatment of refractory depression. *J Clin Pharmacol.* 1981 Aug-Sep;21(8-9):351-8.
24. Sobiś J, Jarzab M, Hese RT, Sieroń A, Zyss T, Gorczyca P, et al. Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression. *Journal of Affective Disorders.* 2010;123(1-3):321-6.
25. Teodor Hese R, Jedrzejewska B. Multiple EEG examinations in patients with recurrent, refractory major depression and bipolar depression after course of UECT. *Archives of Psychiatry and Psychotherapy.* 2000 Sep 2000;2(3):17-24.

26. Thase ME, Greenhouse JB, Frank E, Reynolds CF, 3rd, Pilkonis PA, Hurley K, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry*. 1997 Nov;54(11):1009-15.
27. Trivedi MH, Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. *Arch Gen Psychiatry*. 2004 Jul;61(7):669-80.
28. Williams MD, Rummans T, Sampson S, Knapp R, Mueller M, Husain MM, et al. Outcome of electroconvulsive therapy by race in the Consortium for Research on Electroconvulsive Therapy multisite study. *J Ect*. 2008 Jun;24(2):117-21.
29. Zhang Y, White PF, Thornton L, Perdue L, Downing M. The use of nicardipine for electroconvulsive therapy: a dose-ranging study. *Anesth Analg*. 2005 Feb;100(2):378-81.

Wrong Study Design

1. Amsterdam JD, Garcia-Espana F, Rosenzweig M. Clomipramine augmentation in treatment-resistant depression. *Depress Anxiety*. 1997;5(2):84-90.
2. Bares M, Novak T, Kopecek M, Stopkova P, Sos P. Is combined treatment more effective than switching to monotherapy in patients with resistant depression? A retrospective study. *Neuro Endocrinol Lett*. 2009;30(6):723-8.
3. Black DW, Goldstein RB, Nasrallah A, Winokur G. The prediction of recovery using a multivariate model in 1471 depressed inpatients. *Eur Arch Psychiatry Clin Neurosci*. 1991;241(1):41-5.
4. Bouwer C, Stein DJ. Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression. *S Afr Med J*. 1997 Apr;87(4 Suppl):534-7, 40.
5. Fontaine R, Ontiveros A, Elie R, Vezina M. Lithium carbonate augmentation of desipramine and fluoxetine in refractory depression. *Biol Psychiatry*. 1991 May 1;29(9):946-8.
6. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. 2005 Sep 1;58(5):364-73.
7. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Current Medical Research and Opinion*. 2010;26(10):2475-84.
8. Janssen J, Pol HEH, Schnack HG, Kok RM, Lampe IK, de Leeuw F-E, et al. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. *International Journal of Geriatric Psychiatry*. 2007 05;22(5):468-74.
9. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Archives of General Psychiatry*. 1999 08;56(8):713-8.
10. Nierenberg AA, Papakostas GI, Petersen T, Kelly KE, Iacoviello BM, Worthington JJ, et al. Nortriptyline for treatment-resistant depression. *J Clin Psychiatry*. 2003 Jan;64(1):35-9.
11. Patten SB, Lupin DA, Boucher SA, Lamarre CJ. Pharmacologic management of refractory depression. *Cmaj*. 1992 Feb 15;146(4):483-7.
12. Trivedi MH, Kleiber BA. Using treatment algorithms for the effective management of treatment-resistant depression. *J Clin Psychiatry*. 2001;62 Suppl 18:25-9.

13. Trivedi MH, Thase ME, Osuntokun O, Henley DB, Case M, Watson SB, et al. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry*. 2009 Mar;70(3):387-96.
14. Walter G, Martin J, Kirkby K, Pridmore S. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Aust N Z J Psychiatry*. 2001 Feb;35(1):58-61.
15. Wijkstra J, Nolen WA, Algra A, van Vliet IM, Kahn RS. Relapse prevention in major depressive disorder after successful ECT: a literature review and a naturalistic case series. *Acta Psychiatr Scand*. 2000 Dec;102(6):454-60.

Appendix D. Evidence Tables

Evidence Table 1. KQ1 head to head: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Pridmore, 2000¹</p> <p><i>Country, Setting</i> Australia, University of Tasmania, Psychological Medicine, Royal Hobart Hospital, inpatient and outpatient</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> To determine whether rTMS treatments could be substituted for ECT treatments in a course of ECT, without loss of antidepressant effect, and without increase in subjective side-effects.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study Design</i> RCT</p> <p><i>Type of Analysis</i> ITT</p> <p><i>N</i> 22</p> <p><i>Duration</i> Primary outcome after 2 weeks of txt Interventions G1: ECT Only G2: ECT + rTMS</p> <p><i>Medications Allowed</i> Pts taking antidepressants or mood stabilizers were allowed to continue on these. Not all patients were taking medication at entry. All other psychotropics were ceased 1 week prior to txt initiation</p> <p><i>Parameters</i> ECT: • % receiving bilateral: 0 • Intensity: percentage of 504mC equivalent to age of patient.</p>	<p><i>TRD Definition</i> • 2+ failed ADs from 2+ drug classes (after 1+ month trials at the max manufacturer recommended dose) • Not required to be in current episode</p> <p><i>Tier 1 Inclusion Criteria</i> • MDD DSM-IV • Right-handed • Age 25-70 • Physically well and free of epilepsy and intracranial metal objects • exceed both 26 on MADRS and 18 on HAM-D17</p> <p><i>Exclusion Criteria</i> NR</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, median yrs</i> G1: 47.1 (48) G2: 44.0 (46)</p> <p><i>Sex, % females</i> G1: 54.5% G2: 45.4%</p> <p><i>Right Handed, %</i> 100%</p> <p><i>HAM-D 17</i> Baseline n G1: 11 G2: 11 Baseline score, median (SD) G1: 30 G2: 28</p> <p><i>MADRS</i> Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 40 G2: 40</p>	<p><i>HAM-D 17</i></p> <p>Endpoint score, median (SD) At week 1 G1: 14 G2: 15 At week 2 G1: 7 G2: 8</p> <p>Change, mean (SD) At week 1 G1: -16 G2: -13' <i>P</i> = 0.3</p> <p>At week 2 G1: -23 G2: -20 <i>P</i> = 0.6</p> <p>Remission HAM-D17 < 9 G1: 6 (54.5%) G2: 6 (54.5%) <i>P</i> = NR</p> <p><i>MADRS</i></p> <p>Endpoint score, mean (SD)</p>	<p><i>Quality of Life</i> Global Assessment of Functioning (GAF) Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 41 G2: 41</p> <p>Endpoint score, mean (SD) At week 1 G1: 55 G2: 55 At week 2 G1: 70 G2: 65</p> <p>Change, mean (SD) At week 1 G1: +14 G2: +14 At week 2 G1: +29 G2: +24 • Median scores are reported; none of <i>P</i> values were significant</p>

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Number of sessions (range, mean, SD): 3 times/wk for 2wks rTMS: <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%):100 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval:20 • Pulses per session: 1200 • Total number of sessions: 4/wk with 1 UL ECT Strategy Mixed 		<p><i>Responders, n</i> Baseline n G1: 11 G2: 11 Baseline score, mean (SD) G1: 9.3 G2: 8.3</p>	<p>At week 1 G1: 17 G2: 20 At week 2 G1: 12 G2: 11</p> <p>Change, mean (SD) At week 1 G1: -23 G2: -20</p> <p>$P = 0.1$ At week 2 G1: -28 G2: -29 $P = 0.5$</p> <p>Responders, n G1: 6 (54.5%) G2: 6 (54.5%)</p> <p>Endpoint score, mean (SD) At week 1 G1: 6.2, G2: 6.4 At week 2 G1: 3.0 G2: 5.0</p> <p>Change, mean (SD) At week 1 G1: -3.1G2: -1.9 At week 2 G1: -6.3 G2: -3.3</p>	<ul style="list-style-type: none"> • Comparison of gains made by ECT vs. ECT + rTMS: Awk 1 = $P = 0.6$, CI -13 - 12, Awk2 = $P = 0.2$, CI -4 - 17, Awk1 +Awk2 = $P = 0.4$, CI = -- 8 - 17 • Median scores are reported; none of P values were significant • Comparison of gains made by ECT vs. ECT + rTMS: Awk 1 = $P = 0.6$, CI -13 - 12, Awk2 = $P = 0.2$, CI -4 - 17, Awk1 +Awk2 = $P = 0.4$, CI = -- 8 - 17. <p><i>Adverse Events</i> Overall, % Positive responses G1: 56 G2: 31</p> <p>Amnesia, % Memory Problems At Week 1 G1: 8 r, G2: 3G1:: 9 G2: 4</p> <p>Headache, responses At Week 1 G1: 8 G2: 5</p>

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>At Week 2 G1: 9 G2: 6</p> <ul style="list-style-type: none"> • None of observed differences in proportions of patients having side effects were statistically significant, as judged by Fisher's exact test • It should be noted that due to small sample sizes, chance of detecting massive differences was small • At both assessments (week 1 and week 2), "memory problems" were more than twice as common inECT only stream compared to ECT + rTMS • Due to small sample sizes, statistical tests cannot exclude possibility that difference is due to chance. <p>muscle pains</p> <ul style="list-style-type: none"> • ECT group, wk 1 = 7 responses, wk 2 = 6 responses; ECT + rTMS, wk 1 = 4, wk 2 = 4. <p><i>Attrition</i> NR</p>

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Rosa et al., 2006²</p> <p><i>Country, setting</i> Brazil, university clinic, inpatients and outpatients included</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Included completers analysis & ITT (LOCF), ITT is reported in abstraction</p> <p><i>N</i> 42</p> <p><i>Duration</i> Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medications allowed</i> ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed</p> <p><i>Strategy</i> Switch</p>	<p><i>TRD definition</i> • A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) • Not required or not specified to be in current episode</p> <p><i>Tier 1 Inclusion criteria</i> • Age 18-65 • unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms</p> <p><i>Exclusion criteria</i> • History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease • Use of cardiac pacemaker • Pregnancy</p>	<p><i>Treatment Failure</i> Previous treatment, not specified, % Overall:100%</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 46.0 G2: 41.8</p> <p><i>Sex, % females</i> G1: 46.7 G2: 60.0</p> <p><i>Race, % white</i> G1: 80.0 G2: 90.0</p> <p><i>HAM-D 17</i> Baseline n G1: 20 G2: 22 Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20]</p> <p><i>CGI</i> Baseline n G1: 20 (N analyzed =15) G2: 22 (N analyzed =20)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) NR (graph only)</p> <p><i>Change, mean (SD)</i> NR (graph only) <i>P</i> = 0.86</p> <p><i>Responders, n (%)</i> G1: 6 (20) G2: 10 (45) <i>P</i> = 0.35</p> <p><i>Remitters, n (%)</i> Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) <i>P</i> = 0.65</p> <p><i>Instrument</i> CGI Endpoint score, mean (SD) 2wk G1: 4.0 (1.0) G2: 3.7 (1.1) 4wk G1: 3.2 (1.5) G2: 3.1 (1.3)</p> <p><i>Change, mean (SD)</i> NR, <i>P</i> = 0.672</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR Suicidality, % G1: 10.0 G2: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study</p> <p><i>Neuropsychological or executive functioning</i> • NS differences between groups on all neuropsychological tests following wk2 & wk4. (Wechsler Adult Intelligence Scale - R subtests (Vocabulary, Cube), • Wechsler Memory Scale subtest (Digit Span), • Rivermead Behavioral Memory Test)</p> <p><i>MMSE</i> NR</p>

Evidence Table 1. KQ1 head to head: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>rTMS:</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5) 		<p>Baseline score, mean (SD)</p> <p>G1: 4.7 (0.8)</p> <p>G2: 4.3 (0.8)</p>		<p><i>Other Attrition</i></p> <p>Overall, % 16.7</p> <p>At end of treatment, % G1: 15.0* G2: 9.1*</p> <p>*Prior to completing txt (txt end date differed by pt)</p> <p>At end of follow-up, % G1: 25.0 G2: 9.1</p> <p>Withdrawals due to efficacy, % G1: NR G2: 0.0</p> <p>Withdrawals due to adverse events, % G1: NR G2: 9.1</p> <p>Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 2. KQ1 head to head: Tier 2

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Grunhaus et al., 2003³</p> <p><i>Country, setting</i> Israel, single center, inpatients and outpatients</p> <p><i>Funding</i> National Association for Research in Schizophrenia and Affective Disorders & Stanley Foundation</p> <p><i>Research Objective</i> To compare antidepressant efficacy of rTMS and ECT in nonpsychotic major depression</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> cannot tell, all reported patients included in analysis</p> <p><i>N</i> 40</p> <p><i>Duration</i> Primary outcome after 4 weeks of txt</p> <p><i>Medications Allowed</i> Patients in both groups required to taper psychotropic medications. Only lorazepam allowed regularly, benzodiazepine allowed only for sleep induction</p> <p><i>Strategy</i> Switch Interventions G1: ECT G2: rTMS</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 10 • Motor threshold</p>	<p><i>TRD definition</i> All pts referred for ECT following a failure of 1+ AD (at adequate levels and for at least 4 weeks of txt)</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Age 18+ • Unipolar major depression (DSM IV) • HAM-D \geq 18</p> <p><i>Exclusion criteria</i> • Any exclusion criteria for safety of rTMS • major depression was secondary to a general medical condition or substance abuse • pts with additional Axis I diagnoses</p>	<p><i>Treatment Failure</i> Failed 2 or more, % G1: 60 G2: 65</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 61.4 G2: 57.6</p> <p><i>Sex, % females</i> G1: 75 G2: 70</p> <p><i>HAM-D 17</i> Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 25.5 (5.9) G2: 24.4 (3.9)</p>	<p><i>HAM-D 17</i></p> <p>Endpoint score, mean (SD): At week 2 G1: 15.9 (6.6) G2: 14.7 (8.8) At week 4 G1: 13.2 (6.6) G2: 13.3 (9.2)</p> <p>Change, mean (SD) At week 2 G1: -9.6 G2: -9.7 At week 4 G1: -12.3 G2: -11.1</p> <p>Responders, n Response defined as a decrease \geq 50% or HAM-D17 score \leq 10 and a GAF rating \geq 60 G1: 12 (60%) G2: 11 (55%) P = NS</p> <p>Remitters, n HAM-D17 \leq 8 G1: 6 (30%) G2: 6 (30%) P = NS</p>	<p><i>Quality of Life</i></p> <p>Scale GAF Baseline n G1: 20 G2: 20 Baseline score, mean (SD) G1: 39.8 (9.3) G2: 48.9 (10.8)</p> <p>Endpoint score, mean (SD) At week 2 G1: 55 (12.4) G2: 58.3 (17.1) At week 4 G1: 60.6 (13.5) G2: 62.5 (18.8)</p> <p>Change, mean (SD) b-week 2 G1: -15.2 G2: -9.4 b-week 4 G1: -20.8 G2: -13.6</p> <p>Scale Pittsburgh Sleep Quality Index Baseline n G1: 20 G2: 20</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	(%):90 • Number of trains: 20 • Length of train (seconds): 6 • Inter-train interval:60 • Pulses per session:1200 • Total number of sessions: 5/ wk over 4 wks ECT: • % receiving bilateral: 35 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 10.25 (3.1)				Baseline score, mean (SD) G1: 12.2 (4.5) G2: 10.4 (4.6) Endpoint score, mean (SD) At week 2 G1: 8.3 (3.9) G2: 9.9 (5.1) At week 4 G1: 8.6 (4.9) G2: 9.4 (5.0) Change, mean (SD) b- week 2 G1: 3.9 G2: 0.5 B week 4 G1: 3.6 G2: 1.0 <i>Adverse Events</i> Overall, % G1: NR "the ECT group was handled clinically and no special recording of side effects was done G2: NR Headache, % G1: NR G2: 15.0 Sleep disturbance: G1: NR G2:10%

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Neuropsychological or executive functioning Measures, Results Predefined</i></p> <p>MMSE Baseline n G1: 20 G2: 20</p> <p>Baseline score, mean (SD) G1: 25.8 (3.4) G2: 27.8 (3.0)</p> <p>Endpoint score, mean (SD) At week 2 G1: 26.3 (2.9) G2: 28.0(2.1)</p> <p>At week 4 G1: 27.1(2.5) G2: 28.0 (1.8)</p> <p>Change, mean (SD) b-week 2 G1: -0.5 G2: -0.2</p> <p>b-week 4 G1: -1.3 G2: -0.2</p> <p><i>Attrition</i> NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Kocsis, 2009⁴ Kocsis</p> <p><i>Country, setting</i> United States Multicenter- REVAMP Study</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To determine the role of adjunctive psychotherapy in the treatment of chronically depressed patients with less than complete response to an initial medication trial</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers or per protocol (PP)</p> <p><i>N</i> 491</p> <p><i>Duration</i> Phase I (Medication Algorithm)Only: 12 wks Phase II (Randomization Phase Meds & psychotherapy): 12 wks Primary outcome measure: HAMD and CGI Remission performed biweekly</p> <p><i>Interventions</i> Antidepressant Only Antidepressant + Brief Supportive Psychotherapy Antidepressant + Cognitive behavioral analysis System of Psychotherapy G1: MEDS Only G2: MEDS + Psychotherapy G3: MEDS + Brief Supportive Psychotherapy G4: MEDS + Cognitive Behavioral Analysis</p>	<p><i>TRD definition</i> • For entry into the randomization phase of study pts had to participate in open-label phase of antidepressant algorithm and had to achieve less than remission (remission defined as $\geq 60\%$ reduction in HAMD score, HAMD total score < 8, and no longer meeting DSM-IV criteria for MDD). • Required failure in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • MDE ≥ 4 wks and depressive symptoms for more than 2 yrs without remission; Diagnosis of double depression, chronic major depression, recurrent depression with incomplete recovery between episodes; 18-75 yo; HAM-D24 score ≥ 20; English speaking; informed consent; understanding of the nature of the study</p>	<p><i>Subgroups</i> Chronic Depression</p> <p><i>Baseline n</i> G1: 96 G2: 395 G3: 195 G4: 200</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 100 G2: 100 G3: 100 G4: 100</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 100 G3: 100 G4: 100</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 43.2 G2: 45.9 G3: 46.4 G4: 45.3 G1: vs. G2: p = 0.05</p> <p><i>Sex, % females</i> G1: 49.0 G2: 57.0 G3: 57.9 G4: 56.0</p>	<p><i>HAM-D (Insert #)</i> Yes HAMD24 G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP</p> <p><i>N analyzed</i> Baseline G1: 94 G2: 384 G3: 189 G4: 195 Week 2: G1: 92 G2: 370 G3: 181 G4: 189 Week 4: G1: 85 G2: 359 G3: 176 G4: 183 Week 6: G1: 80 G2: 346 G3: 170 G4: 176 Week 8: G1: 84 G2: 341 G3: 168 G4: 173 Week 10: G1: 79 G2: 333</p>	<p><i>Quality of Life</i> Yes</p> <p>Scale Longitudinal Interval Follow-up Evaluation Range of Impaired Functioning Tool (LIFE-RIFT) Intervention G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP</p> <p>Baseline n Baseline G1: 77 G2: 306 G3: 154 G4: 152 Week 4: G1: 81 G2: 342 G3: 171 G4: 171 Week 8: G1: 80 G2: 326 G3: 162 G4: 164 Week 12: G1: 75 G2: 334 G3: 162 G4: 172</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>System of Psychotherapy (CBASP) G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP</p> <p>G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP</p> <p><i>Medications Allowed</i> Next step medication in the following sequence: Sertraline; escitalopram, ibuproprion, venlafaxine, mirtazapine, and/or lithium augmentation During first 4 weeks, if intolerant moved to next level of sequence</p> <p><i>Strategy</i> Combination</p> <p><i>Parameters</i> G1: Meds only G2: Meds + plus either CBASP or BSP G3: Meds + BSP: includes, reflective listening, empathy, evoking affect, therapeutic optimism, and acknowledgment of</p>	<p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Pregnancy; current diagnosis of any psychotic disorder, history of bipolar disorder; dementia; principal diagnosis of PTSD, AN, BN, OCD; antisocial, schizotypal or severe borderline personality disorder; current alcohol or other substance-related dependence requiring detoxification (exception nicotine dependence); previous treatment with cognitive behavioral analysis system of psychotherapy (CBASP) failing at least 4 of the treatment steps in pharmacotherapy algorithm; unwilling to terminate other forms of psychiatric treatment; serious unstable or terminal medical illness 	<p><i>Race, % white</i> G1: 85.4 G2: 89.6 G3: 89.2 G4: 90.0 G1: vs. G2, p = 0.03</p> <p><i>Not Specified, %</i> G1: NR G2: NR G3: NR G4: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR G3: NR G4: NR</p> <p><i>Groups similar at baseline</i> There were small but statistically significant differences in Race (p = 0.03) and Age (p = 0.05) in the MEDS only vs. MEDS +Psychotherapy comparison.</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 18.37 (8.00) G2: 19.48 (8.27) G3: 19.44 (8.31) G4: 19.52 (8.26)</p>	<p>G3: 163 G4: 170 Week 12: G1: 76 G2: 342 G3: 168 G4: 174</p> <p>Endpoint score, mean (SD) Week 2: G1: 16.82 (9.21) G2: 17.87 (8.55) G3: 18.14 (8.99) G4: 17.61 (8.13) Week 4: G1: 15.27 (9.46) G2: 17.09 (8.49) G3: 17.24 (8.04) G4: 16.94 (8.92) Week 6: G1: 13.74 (7.97) G2: 15.55 (8.65) G3: 16.28 (8.70) G4: 14.85 (8.57) Week 8: G1: 13.71 (8.54) G2: 14.74 (8.45) G3: 15.08 (8.26) G4: 14.42 (8.65) Week 10: G1: 13.66 (8.52) G2: 14.04 (8.90) G3: 14.94 (9.38) G4: 13.18 (8.36) Week 12: G1: 12.28 (8.44) G2: 12.02 (8.39)</p>	<p>Baseline score, mean (SD) G1: 12.64 (3.01) G2: 12.70 (3.05) G3: 12.71 (3.14) G4: 12.69 (2.96)</p> <p>Endpoint score, mean (SD) Week 4: G1: 12.07 (3.54) G2: 11.96 (3.15) G3: 12.13 (3.15) G4: 11.78 (3.14) Week 8: G1: 11.15 (3.33) G2: 11.50 (3.29) G3: 11.76 (3.28) G4: 11.25 (3.30) Week 12: G1: 10.96 (3.63) G2: 10.48 (3.36) G3: 10.73 (3.46) G4: 10.24 (3.25)</p> <p>Change, mean (SD) At wk 12, Calculated: G1: -1.68 G2: -2.22 G3: -1.98 G4: -2.45</p> <p>Other Mixed-effects linear regression: G1: vs. G2, p = 0.31 G3 vs. G4, p = 0.09</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>patients' assets; specific interpersonal, cognitive, behavioral, and psychodynamic interventions were strictly proscribed; Administered for 16 -20 sessions during 12 wks of treatment. G4: Meds + CBASP: structured CBT with a structured interpersonal problem-solving algorithm; Administered twice weekly during weeks 1 - 4 and weekly through wks 5 -12; 16 total sessions.</p>			<p>G3: 12.77 (8.45) G4: 11.29 (8.30) Change, mean (SD) At 12 weeks, calculated: G1: -6.09 (NR) G2: -7.46 (NR) G3: -6.67 (NR) G4: -8.23 (NR)</p> <p>Responders, n Partial Response Week 2 G1: 6 G2: 33 Week 4 G1: 9 G2: 31 Week 6 G1: 8 G2: 48 Week 8 G1: 9 G2: 51 Week 10 G1: 8 G2: 53 Week 12 G1: 16 G2: 89 Full Response Week 2 G1: 7 G2: 9 Week 4 G1: 10 G2: 22 Week 6 G1: 13</p>	<p>Interaction between treatment and time: G1: vs. G2, p = 0.27 G3 vs. G4, p = 0.52</p> <p>Scale Intervention Baseline n Baseline score, mean (SD) Endpoint score, mean (SD) Change, mean (SD) Other <i>Adverse Events</i> Overall, % NR Amnesia, % NR Cardiovascular adverse events, % NR Cognitive impairment, % NR Dizziness, % NR</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: 31 Week 8 G1: 13 G2: 47 Week 10 G1: 13 G2: 57 Week 12 G1: 11 G2: 52 Remitters, n Week 2 G1: 17 G2: 46 G3: 26 G4: 20 Week 4 G1: 24 G2: 50 G3: 21 G4: 29 Week 6 G1: 23 G2: 71 G3: 30 G4: 41 Week 8 G1: 23 G2: 76 G3: 33 G4: 43 Week 10 G1: 21 G2: 89 G3: 39 G4: 50 Week 12	Headache, % NR Insomnia, % NR Post op complications, % NR Somnolence, % NR Suicidality, % NR Additional Comments NA Utilized the Frequency, Intensity and Burden of Side Effects Rating form: Moderate Intensity (% of patients): G1: 17.7 G2: NR G3: 27.0 G4: 26.2 Moderate burden (% of patients): G1: 8.3 G2: NR G3: 11.8 G4: 14.0 <i>Neuropsychological or executive functioning</i> No

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G1: 30 G2: 119 G3: 52 G4: 67</p> <p>Other Response: Categorical status as remitter, nonresponder or partial responder. Remitter: HAM-D score of < 8 that had decreased by at ≥ 50% from baseline and having a CGI score of 1 or 2 for 2 consecutive visits. Partial responder: having Ham-d score of 8-16 that had decreased by at ≥ 50% from baseline and having a CGI score of ≤ 3 or HAM-D score of < 8 and CGI of 1 or 2 for 1 wk but not 2 consecutive wks Nonresponder: not meeting criteria of remitter or a partial responder. Mixed-effects linear regression analysis: G1: vs. G2, p = 0.67 G3 vs. G4, p = 0.04 Mixed-effects ordinal logistic regression analyses:</p>	<p>Measures, Results NR</p> <p>Predefined Yes</p> <p>MMSE No</p> <p>Baseline n</p> <p>Baseline score, mean (SD)</p> <p>Endpoint score, mean (SD)</p> <p>Change, mean (SD)</p> <p>Other</p> <p>Other Yes Utilized the Frequency, Intensity and Burden of Side Effects Rating form: Moderate Intensity (% of patients): G1: 17.7 G2: NR G3: 27.0 G4: 26.2 Moderate burden (% of patients): G1: 8.3 G2: NR G3: 11.8</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G1: vs. G2, p = 0.39 G3 vs. G4, p = 0.06 Treatment x time interaction: G1: vs. G2:, p = 0.03 G3 vs. G4, p = 0.79 HAMD Remission (<8) G1: 30 (31.3) G3: 52 (26.7) G4: 67 (33.5) P = NR</p> <p><i>QIDS</i> Intervention G1: MEDS only G2: MEDS + Psychotherapy G3: BSP G4: CBASP</p> <p><i>N analyzed</i> G1: 89 G2: 365 G3: 179 G4: 186 Week 2: G1: 88 G2: 347 G3: 170 G4: 177 Week 4: G1: 81 G2: 351 G3: 171 G4: 180 Week 6: G1: 75 G2: 336</p>	<p>G4: 14.0</p> <p>Adequate information Yes <i>Attrition</i> Overall, % 13.8</p> <p>At end of treatment, % G1: 16.6 G2: 13.2 G3: 13.8 G4: 12.5</p> <p>At end of followup, % G1: NA G2: NA G3: NA G4: NA</p> <p>Withdrawals due to efficacy, % G1: 5 (5.2%) G2: 5 (1.3%) G3: 4 (2.1%) G4: 1 (0.5%)</p> <p>Withdrawals due to adverse events, % G1: 2 (2.1%) G2: 3 (0.8%) G3: 1 (0.5%) G4: 2 (1.0%)</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G3: 166 G4: 170 Week 8: G1: 82 G2: 326 G3: 161 G4: 165 Week 10: G1: 77 G2: 323 G3: 154 G4: 169 Week 12: G1: 73 G2: 330 G3: 162 G4: 168</p> <p>Baseline score, mean (SD) G1: 10.16 (4.50) G2: 10.85 (4.77) G3: 10.89 (4.79) G4: 10.82 (4.76)</p> <p>Endpoint score, mean (SD) Week 2: G1: 9.10 (5.19) G2: 9.90 (4.64) G3: 10.20 (4.88) G4: 9.60 (4.39) Week 4: G1: 8.49 (5.51) G2: 9.27 (4.65) G3: 9.50 (4.65) G4: 9.04 (4.66)</p>	<p>Other NOTE: Study compares G1: vs. G2 and G3 vs. G4; G3 and G4 make up G2.</p> <p><i>Adherence/ compliance</i> Adherence Number of Sessions attended: mean (SD, Range) G3: 13.2 (7.0, 0 - 21) G4: 12.6 (6.7, 0 - 19) Association of # of sessions attende and probability of remission: G3: 1.01, p = 0.62) G4: 1.02, p = 0.43)</p>

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Week 6: G1: 7.69 (4.56) G2: 8.81 (4.76) G3: 9.25 (4.97) G4: 8.38 (4.52)</p> <p>Week 8: G1: 7.95 (5.12) G2: 8.27 (4.60) G3: 8.47 (4.59) G4: 8.08 (4.60)</p> <p>Week 10: G1: 7.60 (4.61) G2: 7.62 (4.83) G3: 8.03 (4.89) G4: 7.25 (4.77)</p> <p>Week 12: G1: 7.49 (5.24) G2: 6.96 (4.59) G3: 7.30 (4.41) G4: 6.63 (4.76)</p> <p>Change, mean (SD) Calculated: G1: -2.67 (NR) G2: -3.89 (NR) G3: -3.58 (NR) G4: -4.19 (NR)</p> <p>Other Remission defined as having a total score of 6. Significance NR Remission, #: Week 2 G1: 24 G2: 64 G3: 32 G4: 32</p>	

Evidence Table 2. KQ1 head to head: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 4 G1: 29 G2: 94 G3: 45 G4: 49 Week 6 G1: 27 G2: 93 G3: 43 G4: 50 Week 8 G1: 28 G2: 101 G3: 47 G4: 54 Week 10 G1: 32 G2: 126 G3: 56 G4: 70 Week 12 G1: 32 G2: 152 G3: 67 G4: 85	

Evidence Table 3. KQ1 head to head: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Chistyakov et al., 2005⁵</p> <p><i>Country, setting</i> Israel, single psychiatry department, inpatients</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To investigate changes in cortical excitability following ECT in patients with major depression (MD) and to compare therapeutic efficacy of ECT combined with rTMS to that of ECT alone.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell type of analysis – all reported patients included</p> <p><i>N</i> 22</p> <p><i>Duration</i> Primary outcome at 3 weeks Interventions G1: ECT+ rTMS G2: ECT + placebo</p> <p><i>Medications Allowed</i> All antidepressants were tapered and discontinued 1 week before start and no patients received anticonvulsant mood stabilizers</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> ECT: • % receiving bilateral: 100 • Intensity: NR</p>	<p><i>TRD definition</i> Patients referred for ECT, AD failures were not required.</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • DSM IV criteria for major depression • age was between 20 and 75 years</p> <p><i>Exclusion criteria</i> • Suicidal risk • any central or peripheral nervous system disease, • seizure disorder, • history of head trauma in last year, • systemic uncontrolled disease, • pacemaker or metallic implants • drug or alcohol abuse</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 59.2 G2: 54.0</p> <p><i>Sex, % females</i> G1: NR G2: NR</p> <p><i>Overall: 68</i></p> <p><i>HAM-D</i> Baseline n G1: 12 G2: 10</p> <p><i>Baseline score, mean (SD)</i> Reported in graph only</p>	<p><i>HAM-D</i> Endpoint score, mean (SD)NR</p> <p><i>Change, mean (SD)</i> NR Group x time, $P > 0.05$</p> <p><i>Responders, n</i> G1: NR G2: NR</p> <p><i>Overall: 19 (86%)</i> $P = \text{NR (ns)}$</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p><i>Measures, Results</i> NR</p> <p><i>Predefined</i> No</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Number of sessions (range, mean, SD): 2/wk rTMS • Frequency (Hz):1 • Motor threshold (%):110 • Number of trains: NR • Length of train (seconds): NR • Inter-train interval: NR • Pulses per session: 900 • Total number of sessions: 4/wk for 3 weeks Sham rTMS • Coil was held perpendicularly to scalp surface. • Patients received 4 sessions/wk 				
<p><i>Author, Year</i> Hansen, 2010⁶ Hansen</p> <p><i>Country, setting</i> Denmark University Hospital Inpatient Psychiatric</p> <p><i>Funding</i> Danish Council for Medical Research; Einar Geert-Jorgensen and Wife Ellen Geert-Jorgensen Research Foundation; Boutcher Worzner and wife Inger</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT PP</p> <p><i>N</i> 60</p> <p><i>Duration</i> Active treatment: 3 wks HAM-D and UKU assessed at baseline and weekly intervals w/in 24 hrs of treatment</p>	<p><i>TRD definition</i> • Patients referred for ECT</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • 18-80 yo; HAM-D-17 total score of ≥ 20 and/or subscale score of ≥ 9; right-handed; ICD-10 diagnosis of moderate to severe depression; DSM-IV diagnosis of MDD; unipolar or bipolar</p>	<p><i>Subgroups</i> No Subgroups</p> <p><i>Baseline n</i> G1: 30 G2: 30</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: NR G2: NR</p> <p>Failed 2 or more, % G1: NR G2: NR</p>	<p><i>HAM-D (Insert #)</i> Yes HAM-D17 G1: rTMS G2: ECT</p> <p>Endpoint score, mean (SD) Week 3 G1: NR Baseline - wk3 reduction, $p < 0.001$ G2: NR</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Worzner grant; the Aarhus University Foundation for Research in Mental Disease; the Foundation of Psychiatric Research Research Objective</p> <p>To compare the antidepressant efficacy and adverse effects of right prefrontal low-frequency rTMS with that of ECT.</p> <p><i>Quality Rating</i> Fair - KQ1 KQ4?</p>	<p>Follow-up treatment: 7 wks (total duration) HAMD and UKU assessed at wk 5 and wk 7</p> <p><i>Interventions</i> ECT rTMS G1: rTMS G2: ECT</p> <p><i>Medications Allowed</i> Continued current antidepressant medication; discontinued antiepileptics prescribed as mood stabilizers, benzodiazepines tapered off, low dose zopiclone or zopidem if needed for sleep</p> <p><i>Strategy</i> Augment or add-on strategy</p> <p><i>Parameters</i> G1: Location: Right DLPFC Frequency: 1 Hz Intensity: 110% MT Trains: 2 60s trains Intertrain interval: 180 s Number of session: 15 total (1 per week day for</p>	<p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Organic brain damage; personal/family history of epileptic seizures, metallic objects in the chest or brain as a result of surgery; cardiac pacemakers; somatic diseases associated w/ brain dysfunction; pregnancy; use of coercive measures; suicidal risk of severe degree; severe agitation; delirium; alcohol or drug dependence. 	<p>Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: 86.7 G2: 86.7</p> <p>Bipolar I G1: 13.3 G2: 13.3</p> <p>Bipolar II G1: NR G2: NR</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> Median (range) G1: 46 (14-38) G2: 52 (29-79) p = 0.16</p> <p><i>Sex, % females</i> G1: 76.7 G2: 63.3</p> <p><i>Race, % white</i> G1: NR G2: NR</p>	<p>Baseline - wk3 reduction, p <0.001 Week 3-7 G1: NR G2: NR wk3 - wk7 reduction, p <0.001 G1: NR G2: NR wk3 - wk7 reduction, p = 0.78 Week 7 G1: NR G2: NR Baseline - wk 7 reduction, p < 0.001 G2: NR Baseline - wk 7 reduction, p < 0.001</p> <p>Change, mean (SD) G1: NR G2: NR</p> <p>Responders, n Response Rate Difference Week 3, Rate (95% CI): G1: 0.20 (0.08-0.39) G2: 0.57 (0.37-0.75) G1: vs. G2 rate difference: 0.37 (0.14-0.59), p = 0.003 Week 7, Rate (95%CI): G1: 0.43 (0.25-0.63) G2: 0.60 (0.41-0.77) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200</p>	<p>Cognitive impairment, % G1: 0 G2: 0</p> <p>Dizziness, % NR Headache, % NR</p> <p>Insomnia, % NR</p> <p>Post op complications, % NR Somnolence, % Significantly > decline in fatigue score in the ECT group (score NR)</p> <p>Suicidality, % NR</p> <p>Additional Comments NR "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience.</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>3 weeks) G2: Location: Unilaterally over the right hemisphere Intensity: Recorded seizure duration ≥ 25 seconds; If between 15-25 seconds next treatment carried out with 50% higher stimulus intensity; If < 15 seconds then followed by restimulation. Number of session: 9 total (3 sessions weekly)</p>		<p><i>Not Specified, %</i> G1: NR G2: NR <i>Right handed, %</i> G1: 100 G2: 100 Groups similar at baseline Yes <i>HAM-D 17</i> Baseline score, mean (SD) Median (Range): G1: 24 (14-38) G2: 24 (16-34) G1: vs. G2: p = 0.68</p>	<p>Remitters, n Remission Rate Difference Week 3 Rate (95% CI): G1: 0.27 (0.12 - 0.46) G2: 0.53 (0.34 - 0.72) G1: vs. G2 rate difference: 0.26 (0.03 - 0.51), p = 0.035 Week 7 Rate (95% CI): G1: 0.40 (0.23 - 0.59) G2: 0.57 (0.37 - 0.75) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200 Other Remission: HAMD-17 ≤ 12 Response: ≥ 50% reduction in HAMD-17</p>	<p>Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale. <i>Neuropsychological or executive functioning</i> Yes Measures, Results Logical Memory – Immediate recall Baseline, Mean (SD): G1: 10.8 (4.4) G2: 10.0 (5.1) After Treatment G1: 8.8 (3.8) G2: 9.6 (5.1) Logical Memory – Delayed recall Baseline, Mean (SD): G1: 7.6 (5.4) G2: 7.46 (5.5) After Treatment G1: 7.2 (3.7) G2: 6.8 (5.8) Verbal Learning – Total Baseline, Mean (SD) G1: 8.2 (1.7)</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G2: 8.4 (2.1) After Treatment G1: 8.1 (2.0) G2: 7.9 (1.5) Verbal Learning – delayed recall Baseline, Mean (SD) G1: 5.9 (2.3) G2: 5.5 (2.0) After Treatment G1: 6.0 (2.6) G2: 4.8 (3.1) Rey Complex Figure – copy Baseline, Mean (SD) G1: 32.9 (4.2) G2: 29.7 (7.4) After Treatment G1: 33.6 (2.2) G2: 29.2 (6.8) Rey Complex Figure – delayed recall Baseline, Mean (SD) G1: 16.0 (6.2) G2: 13.9 (7.2) After Treatment G1: 25.6 (7.4) G2: 13.1 (9.4) G1: vs. G2, p <0.01 Within groups, p <0.01 Trail-Making Test A Baseline, Mean (SD) G1: 65.7 (35.5) G2: 64.7 (23.5) After Treatment G1: 60.6 (39.4) G2: 65.9 (34.0) Trail-Making Test B

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Baseline, Mean (SD) G1: 147.8 (64.4) G2: 131.3 (50.1) After Treatment G1: 131.0 (68.0) G2: 107.8 (36.0) SDMT Baseline, Mean (SD) G1: 29.9 (12.0) G2: 29.3 (13.7) After Treatment G1: 34.0 (12.6) G2: 31.1 (14.0) Verbal Fluency – letter S Baseline, Mean (S) G1: 10.4 (3.8) G2: 11.6 (7.3) After Treatment G1: 12.9 (5.6) G2: 10.3 (6.1) Verbal Fluency – animals Baseline, Mean (SD) G1: 18.4 (6.3) G2: 16.3 (4.5) After Treatment G1: 19.8 (6.2) G2: 14.11 (3.1) G1: vs. G2, p < 0.05</p> <p>Other Yes "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients,</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale.</p> <p>Adequate information Yes</p> <p><i>Attrition</i> Overall, % 30</p> <p>At end of treatment, % G1: 33.3 G2: 26.7</p> <p>At end of followup, % G1: NR G2: NR</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Withdrawals due to efficacy, % G1: NR G2: NR</p> <p>Withdrawals due to adverse events, % G1: NR G2: NR Other</p> <p>Withdrawal due to Discomfort at the stimulus site, % (n): G1: 16.7 (5) G2: 0 (0)</p> <p>Withdrawal due to serious deterioration, % (n): G1: 10 (3) G2: 3 (1)</p> <p>Withdrawal due to somatic disease, % (n): G1: 3 (1) G2: 0 (0)</p> <p>Withdrawal due to Commotio cerebri, % (n): G1: 0 (0) G2: 3 (1)</p> <p>Withdrawal for unknown reasons, % (n): G1: 0 (0) G2: 3 (1)</p> <p><i>Adherence/ compliance</i> None reported</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> McLoughlin et al., 2007⁷ Eranti et al., 2007⁸ Knapp et al., 2008⁹</p> <p><i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital in Invicta Mental Health Trust in Kent, 65.2% were inpatients</p> <p><i>Funding</i> National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating major depressive episodes in patients referred for ECT</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters)</p> <p><i>Type of analysis</i> m-ITT</p> <p><i>N</i> 46</p> <p><i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p> <p><i>Strategy</i> Augmentation</p>	<p><i>TRD definition</i> • All patients referred for ECT: • No failure required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Right handed patients • more than 18 years old • referred for ECT due to major depressive episode</p> <p><i>Exclusion criteria</i> • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.</p>	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % Age, mean yrs G1: 63.6 G2: 68.3 Sex, % females G1: 67.7 G2: 72.7</p> <p><i>Right handed, %</i> Overall: 100%</p> <p><i>HAM-D 17</i> Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)</p> <p><i>BDI:</i> Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p><i>HAM-D 17</i> Analyzed n G1: 22 G2: 23</p> <p>Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 <i>P</i> = 0.002, effect size of 1.44</p> <p>Follow-up at 6 months G1: NR G2: NR <i>P</i> = 0.93</p> <p>Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 <i>P</i> = 0.017</p> <p>Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p>Remitters, n HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5)</p> <p>Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</p> <p>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (<i>p</i> = 0.987). This suggests that treatment by rTMS does not provide any additional</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Quality Rating</i> Good</p>	<p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 			<p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD) NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	<p>gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU 6 mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory)</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>MMSE Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8) Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3) Change, mean (SD): G1: 1.3 G2: -1.3 <i>P</i> < 0.08</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p> <p><i>Attrition</i> Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0</p> <p>At end of follow-up, % NR Withdrawals due to efficacy, %</p>

Evidence Table 3. KQ1 head to head: Tier 3 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> NR

Evidence Table 4. KQ1 active versus control: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰</p> <p><i>Country, setting</i> USA, Single center, University department of psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good</p> <p>Fair for KQ2 and subgroups11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint</p> <p><i>Interventions</i> G1: High-left TMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazapines G1: 26% vs. G2: 24%)</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p><i>Baseline n</i> G1: 35 G2: 33</p> <p><i>Treatment Failure</i></p> <p>Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67)</p> <p>Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 44.3 G2: 44.2</p> <p><i>Sex, % females</i> G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 15.7 G2: 19.8</p> <p>Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time <i>P</i> = 0.002</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) <i>P</i> = 0.008</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) <i>P</i> = 0.033</p> <p>No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse)</p> <p><i>BDI</i> Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Site pain first session sham none (0/33) vs. TMS group, 41% (14/35)15th session sham 3% (1/30) vs. TMS 33% (11/33).</p> <p>The discomfort pain scale ratings (0-4) decreased inTMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, <i>P</i> < 0.001). Changes from baseline in128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any ofemerging symptoms. (Data = NR)</p> <p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT,</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Those stopping medications had to be medication-free for at least 2 weeks All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> Frequency (Hz):10 Motor threshold (%): 110 Number of trains: 32 Length of train (seconds): 5 Inter-train interval: 25-30 Pulses per session: 1600 Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> Identical stimulation parameters Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> history of substance abuse or dependence within past 2 years, antisocial or borderline personality disorder, active suicidal ideation current symptoms of psychosis, Hx of seizure disorder, Hx of closed head injury with loss of consciousness or prior brain surgery any other major psychiatric or medical comorbidity 	<p>Groups similar at baseline Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>	<p>significant group by time interaction ($P = 0.003$)</p>	<p>and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$) no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures. models were refit without interaction term, there was no significant treatment group main effect ($P > 0.05$) evident for any of neuropsychological tests, indicating groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test performances for both groups.</p> <p>No confusion was associated with TMS treatments. GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session.</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Bocchio-Chiavetto et al., 2008¹²</p> <p><i>Country, setting</i> Italy, Conducted at a single psychiatric unit, patient status NR</p>	<p><i>Study design</i> RCT, crossover</p> <p><i>Type of analysis</i> All reported patients included in the analysis</p> <p><i>N</i> 36</p>	<p><i>TRD definition</i> • 2+ failures (8+ weeks at standard doses) from 2+ classes of antidepressants • Required to be in current episode</p>	<p><i>Subgroups</i> Genotypes: 5-HTTLPR (LL or S carriers) BDNF Val66Met (Val/Val or Met carriers) Baseline N</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) G1: 17.5 (6.91) G2: 21.13 (4.53)</p> <p>5-HTTLPR G3: 40.49 (25.27) G4: 8.78 (4.23)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Funding</i> Ministero dlla Sanita RC 2000</p> <p><i>Research Objective</i> To evaluate if rTMS is an effective treatment for TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Duration</i> 5 days of txt (8 week between crossover) Primary endpoint following 1 week of treatment</p> <p><i>Interventions</i> G1: Overall active G2: Overall sham</p> <p><i>5-HTTLPR genotypes</i> G3: LL Active G4: LL Sham G5: S Active G6: S Sham</p> <p><i>BDNF Val66Met</i> G7: Val/Val Active G8: Val/Val Sham G9: Met Active G10: Met Sham</p> <p><i>Medications Allowed:</i> • Patients allowed to continue on typical and atypical psychotics • 24 patients on mono- or combined therapies with SSRIs • 12 on other antidepressants (7 on typical, 5 on atypical antipsychotics) • Mean dose as imipramine equivalents = 148.56 ±49.77</p>	<p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • HAM-D 21 ≥ 17 • TRD</p> <p><i>Exclusion criteria</i> • Pregnancy, major medical, or neurological disorder</p>	<p>G1: 36 G2: 15 G3: 10 G4: 3 G5: 26 G6: 12 G7: 20 G8: 10 G9: 16 G10: 5</p> <p>Treatment Failure Mean failed trials G1: NR G2: NR G3: 2.80 (0.79) G4: NR G5: 2.92 (1.21) G6: NR G7: 2.79 (0.98) G8: NR G9: 3.00 (1.25) G10: NR Overall: 2.89</p> <p><i>Polarity, %</i> MDD G1: 86.1% Bipolar G1: 13.9% Age, mean yrs G1: 59.67 Sex, % females G1: 80.5 Race, % white G1: 100%</p>	<p>G5: 19.44 (17.51) G6: 14.11 (16.86) G3 vs G5, <i>P</i> = 0.008 G4 vs G6, <i>P</i> = 0.605</p> <p>BDNF G7: 32.36 (21.33) G8: 16.52 (10.64) G9: 16.45 (19.90) G10: 6.11 (12.46) G7 vs G9, <i>P</i> = 0.028 G8 vs G10, <i>P</i> = 0.233 Change, mean (SD) G1: -5.69 G2: -3.40 <i>P</i> = NR % Change G1: 25.29% (NR) G2: 13.05% (NR) <i>P</i> = NR</p>	<p>MMSE No</p> <p><i>Attrition</i> NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS Low</p> <ul style="list-style-type: none"> • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 40 • Length of train (seconds):10 • Inter-train interval: 20 • Pulses per session: 400 • Total number of sessions: 5 in 5 days <p>High</p> <ul style="list-style-type: none"> • Frequency (Hz):17 • Motor threshold (%):110 • Number of trains: 8 • Length of train (seconds): 3 • Inter-train interval: 120 • Pulses per session: 408 • Total number of sessions: 5 in 5 days <p>Sham:</p> <ul style="list-style-type: none"> • 25mm thick plywood shield, built to appear as an integral part of apparatus, was 		<p><i>HAM-D 21</i> Baseline score, mean (SD)</p> <p>G1: 23.19 (5.12) G2: 24.53 (4.79) G3: 23.40 (6.64) G4: NR G5: 23.12 (4.56) G6: NR G7: 24.10 (5.60) G8: NR G9: 22.06 (4.34) G10: NR</p>		

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	interposed between the coil itself and scalp, separating the two ones. Ventral surface of coil upside down and stimulus intensity substantially decreased at 60% below motor threshold				
<p><i>Author, Year</i> Boutros et al., 2002¹³</p> <p><i>Country, setting</i> US, Yale School of Medicine and VA-Connecticut, outpatient</p> <p><i>Funding</i> VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer</p> <p><i>Research Objective</i> To provide additional data on efficacy and safety for rTMS as an augment strategy in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 21</p> <p><i>Duration</i> 2 weeks txt; follow up with responders for up to 20 weeks post txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> Pts allowed to continue all current psychotropic meds</p> <p><i>Strategy</i> Augmentation, 3 pts in active and 1 in sham</p>	<p><i>TRD definition</i> • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major Depression • HAM-D25 >= 20</p> <p><i>Exclusion criteria</i> • Suicidality • "Prominent" psychotic symptoms • History of neurological disorders • current drug abuse</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 49.5 G2: 52.0</p> <p><i>Sex, % females</i> G1: 25 G2: 10</p> <p><i>Right handed, %</i> G1: 90.9 G2: 88.9</p> <p><i>HAM-D</i> Baseline n G1: 12 G2: 9</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11</p> <p>Change, mean (SD) G1: -11.75 G2: -6.22 P = NS</p> <p>Responders, n Defined as 30% improvement on HAM-D G1: 7 G2: 2</p> <p>Responders, n (%) Defined as 50% improvement on HAM-D G1: 3 G2: 2</p> <p><i>Relapse</i> Of 6 active treatment responders included</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6</p> <p>Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR</p> <p>Headache, % "most frequent complaint" % NR</p> <p>Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>txt were not on any meds</p> <p><i>Parameters</i> rTMS:</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 58 • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays <p>Sham:</p> <ul style="list-style-type: none"> • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp 		<p>Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)</p>	<p>in20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in thh 20-week follow-up, 1 relapsed.</p>	<p><i>Attrition</i> Overall, % 18.2% (4/22)</p> <p>At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10)</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, %: NR</p> <p>Withdrawals due to adverse events, %: NR</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Fitzgerald et al., 2006¹⁴</p> <p><i>Country, setting</i> Australia, single center</p> <p><i>Funding</i> Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT (LOCF)</p> <p><i>N</i> 50</p> <p><i>Duration</i> 2 wks double blind with those with >20% decrease in MADRS to</p>	<p><i>TRD definition</i> • 2+ failed medications with txt duration ≥6 wks • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • DSM-IV diagnosis of Major Depressive Episode</p>	<p><i>Treatment Failure</i> Mean failed AD trials (lifetime) G1: 5.6 (3.1) G2: 6.2 (3.0)</p> <p><i>Polarity, %</i> Unipolar G1: 84% G2: 84% Bipolar G1: 16% G2: 16%</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) NR Change, % decrease (SD) G1: 45.2% (40.1) G2: 5.4% (23.1) <i>P</i> < 0.001 Change, mean G1: -10.17 G2: -1.07</p>	<p><i>Quality of Life</i></p> <p>GAF Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9) Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [<i>P</i> <0.05] Change, mean (SD)</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald)</p> <p><i>Research Objective</i> rTMS versus placebo for depression</p> <p><i>Quality Rating</i> Good</p>	<p>continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary outcome after 2 and 6 weeks of txt</p> <p>Interventions G1: rTMS G2: Sham</p> <p><i>Medications allowed</i></p> <ul style="list-style-type: none"> • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, • Antipsychotic medication, • Benzodiazepines <p><i>Strategy</i> Augmentation, 23% not taking medication at study entry</p> <p><i>Parameters</i> rTMS Low Right: Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 3</p>	<ul style="list-style-type: none"> • MADRS \geq 20 <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Significant medical illness • Neurological disorders • Other axis I psychiatric disorders 	<p>Age, mean yrs G1: 46.8 G2: 43.7</p> <p>Sex, % females G1: 60 G2: 64</p> <p><i>HAM-D 17</i> Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4)</p> <p><i>BDI</i> Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9)</p> <p><i>MADRS</i> Baseline n G1: 25 G2: 25 Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)</p>	<p>Responders, n (%) At 6wks G1: 13 (52.0) G2: 2 (8.0) $P = 0.001$</p> <p>Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0) $P = \text{NR}$</p> <p><i>BDI</i></p> <p>Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7) At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8) At 6 weeks G1: 9.2 (6.7) G2: NR</p> <p>Change, mean (SD) At week 2 G1: 10.9 G2: 7.7 At 4 weeks G1: 18.7 G2: 8.3 At 6 weeks G1: 20.0 G2: NR, $P = 0.01$</p>	<p>G1: 10.2 G2: 1.1 GAF Scale ($t=2.0$, $df=40.2$, $P < 0.05$)</p> <p><i>Adverse Events</i> Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved on digit span backward test improved in rTMS only (group by time: $P = 0.07$). Controlled Oral Word Association test improved for both groups (time: $P = 0.001$). Nausea 12% vs. 0, No seizures or manic episodes;</p> <p><i>Neuropsychological or executive functioning</i> Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction</p> <p>Digit span backward Test</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 <p>Sequential High Left:</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 • Total number of sessions: 10 sessions/day, 5 days/wk <p>Sham:</p> <ul style="list-style-type: none"> • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides) 			<p>Responders, n NR</p> <p>Remitters, n NR</p> <p><i>MADRS</i> Endpoint score, mean (SD) At week 2 G1: 26.2 (10.2)</p> <p>G2: 30.9 (8.2) At week 4 G1: 11.7 (7.1)</p> <p>G2: 34.5 (12.0) At week 6 G1: 8.9 (7.9) G2: NA</p> <p>Change, mean (SD) At week 2 G1: 7.8 G2: 3.2 At week 4 G1: 22.3</p> <p>G2: 0.4 (increased) At week 6 G1: 25.1 G2: NA</p> <p>Group by time, <i>P</i> = 0.001 at all time points</p>	<p>Performance improved in rTMS only (group by time: <i>P</i> = 0.07).</p> <p>Controlled Oral Word Association Test</p> <p>Improved for both groups <i>P</i> = 0.001</p> <p>MMSE NR</p> <p><i>Other</i> Nausea 12% vs. 0 No seizures or manic episodes;</p> <p><i>Attrition</i> Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78 After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn At end of treatment, % G1: 0 G2: 12 At end of follow-up, % G1: 56 G2: 100</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Responders, n At 6 weeks G1: 11 G2: 2 $P < 0.05$ Remitters, n MADRS < 10 At 6 weeks G1: 9 G2: 0 $P = 0.005$ At week 2 G1: 2 G2: 0 Follow-up at week 3 G1: 3 G2: 0 Follow-up at week 4	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Fitzgerald et al., 2003¹⁵</p> <p><i>Country, setting</i> Australia 2 general psychiatric services, outpatients</p> <p><i>Funding</i> National Health and Medical Research Council and a grant from Stanley Medical</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 60</p> <p><i>Tier 1</i></p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Failed a minimum of 2 courses of antidepressant medications (6+ weeks) Not required or not specified to be in current episode <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> DSM-IV diagnosis of Major Depression 	<p><i>Treatment Failure</i></p> <p>Mean failed trials Overall (SD) 5.68 (3.40)</p> <p>Polarity, %</p> <p>Bipolar I</p> <p>G1: 5 G2: 5 G3: 20</p> <p>Age, mean yrs</p> <p>G1: 42.2 G2: 45.55 G3: 49.15</p>	<p><i>BDI</i></p> <p>Endpoint score, mean (SD)</p> <p>At 2 weeks</p> <p>G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7)</p> <p>Change, mean (SD)</p> <p>At 2 weeks</p> <p>G1- 6.4 G2: -7.8</p>	<p><i>Quality of Life</i></p> <p>GAF Global Assessment of Functioning</p> <p>Baseline n</p> <p>G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD)</p> <p>G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Research Institute</p> <p><i>Research Objective</i> To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group</p> <p><i>Quality Rating</i> Good</p>	<p><i>Duration</i> Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt.</p> <p><i>Interventions</i> G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham</p> <p><i>Medications Allowed</i> 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60</p>	<p>(included bipolar depression)</p> <p><i>Exclusion criteria</i> • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders</p>	<p>Sex, % females G1: 40 G2: 35 G3: 55 Right handed, % G1: 90 G2: 100 G3: 85</p> <p><i>BDI</i> Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)</p> <p><i>MADRS</i> Baseline n G1: 20 G2: 20 G3: 20 Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)</p>	<p>G3: -2.3 <i>P</i> = 0.03</p> <p><i>MADRS</i> Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5)</p> <p>Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) <i>P</i> = 0.004 G1: vs. G3, G2 vs. G3, <i>P</i> < 0.005</p> <p>Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) <i>P</i> = 0.07</p> <p>Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5)</p>	<p>Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8)</p> <p>Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5</p> <p>Overall group <i>F</i>_{56,2}=2.6; <i>P</i> =.08; LFR-TMS vs sham: <i>P</i> = 0.03; and HFLTMS vs sham: <i>P</i> = 0.09</p> <p><i>Quality of Life</i> Overall group <i>F</i>_{56,2}=2.6; <i>P</i> =.08; LFR-TMS vs sham: <i>P</i> = 0.03; and HFLTMS vs sham: <i>P</i> = 0.09</p> <p><i>Adverse Events</i> Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS.</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week <p>rTMS High</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week <p>Sham rTMS</p> <ul style="list-style-type: none"> • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week 			<p>G3: 0 P = NR</p> <p>CGI Endpoint score, mean (SD) NR P =.01</p>	<ul style="list-style-type: none"> • Although there was no difference in incidence of these adverse effects ($P = .08$), patients in HFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence of headache for longer than 1 hour. • Two patients (1 in each group) reported transient dizziness for a short time after treatment. <p>2wks - 4 wks:</p> <ul style="list-style-type: none"> • One patient withdrew after 1 session of HFL-TMS treatment in single-blind phase of study owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium <p><i>Neuropsychological or executive functioning</i></p> <ul style="list-style-type: none"> • No deterioration in performance was found in any cognitive measures in group as a whole or in

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions</p> <ul style="list-style-type: none"> • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on verbal paired associates ($t_{50}=-7.3$; $P < 0.001$), verbal fluency ($t_{48}=-3.8$; $P < 0.001$), and digit span forwards ($t_{48}=-1.8$; $P = 0.003$) subscales; Personal Semantic Memory Schedule ($t_{50}=-2.4$; $P = 0.02$); and Autobiographical Memory Schedule ($t_{50}=-1.9$; $P = 0.05$). • A similar pattern of improvements was seen for each of treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across same times. <p>MMSE NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Other</i></p> <p><i>Attrition</i> Overall, % None in initial 2 week treatment phase</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % NR But at least 28.3% did not continue on thru 2nd 2 weeks</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p><i>Author, Year</i> Garcia-Toro et al., 2001¹⁶</p> <p><i>Country, setting</i> Spain, Inpatient/outpatient status not clearly reported</p> <p><i>Funding</i> NOTE: CANNOT TELL IF FUNDER IS NON-PROFIT. Association for rehabilitation and social integration of mental patients (ARISPAM) & Madrid community physical handicapped Coordinator</p> <p><i>Research Objective</i> To clarify role played by HF-rTMS applied on left DLPC as a coadjuvant top pharmacological treatment of TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 40</p> <p><i>Duration</i> Primary outcome after 2 weeks of treatment. Pts also assessed at 2 weeks follow up post txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham rTMS</p> <p><i>Medications allowed</i> • stable treatment with antidepressants • most pts taking benzodiazepines</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 20 • Motor threshold (%): 90 • Number of trains: 30 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • 2+ failed trials at maximum tolerated dose for 6+ weeks • Required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • 18+ years of age • Unipolar depression (DSM IV)</p> <p><i>Exclusion criteria</i> Previous seizures or neurosurgery, current serious or uncontrolled medical illness, pacemakers, hearing aids, pregnancy or inadequate contraception for females, high suicide risk</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 51.5 G2: 50.0</p> <p><i>Sex, % females</i> G1: 41.2 G2: 44.4</p> <p><i>Right handed, %</i> 100</p> <p><i>HAM-D 17</i> Baseline n G1: 20 G2: 20</p> <p>Baseline score, mean (SD) G1: 27.11 (6.65) G2: 25.6 (4.92)</p> <p><i>BDI</i> Baseline n G1: 20; Analyzed 17 G2: 20; 18</p>	<p><i>HAM-D 17</i> N analyzed G1: 17 G2: 18</p> <p>Change, mean (SD) At week 1 G1: -4.52(4.66) G2: -2.87(4.27) P = 0.297</p> <p>At week 2 G1: -7.05 (5.66) G2: -1.77(3.78) P = 0.003</p> <p>2 week follow up G1: -8.17(7.69) G2: -2.05(6.07) P = 0.013</p> <p>Responders, n (%) G1: 5 (25) G2: 1 (5) P=NR</p> <p><i>BDI</i> Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) At 2 weeks G1: -1.35(4.44) G2: -2.75(4.28) P = 0.299</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Additional Comments</i> "most frequency side effects were scalp discomfort and slight and transitory headaches in approximately a third of cases, nearly all from stimulation group"</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p><i>Measures, Results</i> NR</p> <p><i>Predefined</i> No</p> <p><i>MMSE</i> NR</p> <p><i>Adequate information</i> No</p> <p><i>Attrition</i> Overall, % 12.5 (5/40)</p> <p>At end of treatment, % NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<ul style="list-style-type: none"> • Inter-train interval: 20-40 • Pulses per session: 1200 • Total number of sessions: 10 in 10 days Sham: <ul style="list-style-type: none"> • Edge was placed at 90 degrees 		Baseline score, mean (SD) G1: 27.0 (9.05) G2: 26.38(5.60) CGI-S **CGI subscale not specified inarticle** Baseline score, mean (SD) G1: 476 G2: 4.88	2 week follow up G1: -4.05 (6.72) G2: -1.66(6.89) P = 0.307 CGI-S Change, mean (SD) At week 2 G1: -0.82(0.80) G2: -0.27(0.66) P = 0.04 2 week follow up G1: -1.00(1.17) G2: +0.27(0.95) P = 0.037	At end of follow up, % G1: 15 G2: 10 Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2: Other 3 patients in txt group w/drew because of changes in pharmacotherapy, in sham group: 1 "prefered a change in treatment" andother was abusing alcohol and thus removed fromstudy. <i>Adherence/ compliance</i> NR
<i>Author, Year</i> Garcia-Toro et al., 2006 ¹⁷ <i>Country, setting</i> Spain, single center, all outpatients <i>Funding</i> Fundacio La Marato de TV3	<i>Study design</i> RCT <i>Type of analysis</i> Cannot tell, all reported patients included in analysis <i>N</i> 30	<i>TRD definition</i> <ul style="list-style-type: none"> • Failed 2+ txt trials at 4+ weeks • Not required or not specified to be in current episode <i>Tier 1</i> <i>Inclusion criteria</i> <ul style="list-style-type: none"> • At least 18 yrs old, 	<i>Subgroups</i> None <i>Treatment Failure</i> Mean failed trials NR <i>Polarity, %</i> Unipolar 100%	<i>HAM-D 21</i> Endpoint score, mean (SD) At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10) At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18)	<i>Quality of Life</i> NR <i>Adverse Events</i> NR <i>Attrition</i> Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p><i>Research Objective</i> To assess the efficacy of high and low frequency rTMS and different locations of activation</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Duration</i> • Primary outcome after 2 weeks of active treatment • Follow up: 2 weeks post treatment</p> <p><i>Interventions</i> G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam)</p> <p><i>Medications allowed</i> All pts continued (failed) AD medication and other psychotropic meds</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS Low: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session:</p>	<p>MDD, unipolar</p> <p><i>Exclusion criteria</i> • Contraindications for rTMS and high suicide risk</p>	<p><i>Age, mean yrs</i> G1: 47.2 G2: 48.5 G3: 51.1</p> <p><i>Sex, % females</i> G1: 70 G2: 40 G3: 40</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> G1: 90% G2: 100% G3: 100%</p> <p><i>HAM-D 21</i></p> <p>Baseline n G1: 10 G2: 10 G3: 10</p> <p>Baseline score, mean (SD) G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14)</p> <p><i>CGI-S</i> Baseline n G1: 10 G2: 10 G3: 10</p>	<p>G3: 18.10 (6.15) Follow up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0)</p> <p>Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%)</p> <p>At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), <i>P</i> = 0.048</p> <p>Follow up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%) G1: vs. G2+G3, <i>P</i> = 0.121</p> <p>Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) <i>P</i> = NR</p> <p><i>CGI-S</i> Endpoint score, mean (SD)</p>	<p>pharmacotherapy At end of treatment, % G1: 0 G2: 0 G3: 0</p> <p>At end of followup, % NR Does not report which group 3 patients came from</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission computed tomography (20-Hz rTMS to an area of relatively low activity and 1-Hz rTMS to an area showing relatively high activat</p> <p><i>Adherence/ compliance</i> Compliance all patients completed active 2 week treatment</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p>1800</p> <ul style="list-style-type: none"> Total number of sessions: 10 in 2 wks <p>High</p> <ul style="list-style-type: none"> Frequency (Hz):20 Motor threshold (%): 110 Number of trains: 30 Length of train (seconds): 2 Inter-train interval: 20+5 Pulses per session: 1200 Total number of sessions: 10 in 2 wks <p>Sham</p> <ul style="list-style-type: none"> Same but with coil angling 45 degrees away from scalp 		<p>Baseline score, mean (SD)</p> <p>G1: 4.7 (0.82)</p> <p>G2: 4.8 (1.0)</p> <p>G3: 4.8 (0.63)</p>	<p>At 2 weeks</p> <p>G1: 4.6 (0.97)</p> <p>G2: 3.8 (1.48)</p> <p>G3: 3.9 (0.99)</p> <p>2 week follow up</p> <p>G1: 4.75 (1.16)</p> <p>G2: 4.00 (1.15)</p> <p>G3: 3.7 (1.57)</p>	
<p><i>Author, Year</i> George, 2010¹⁸</p> <p><i>Country, setting</i> United States, outpatient</p> <p><i>Funding</i> NIMH as the Optimization of TMS for the Treatment of Depression Study</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> mITT (all randomized patient who started at least 1 treatment session) Completer (randomized patients who were treated according of protocol and had fewer than 4</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Moderate level of treatment resistance as defined by the ATHF; insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥ 3 trials; <p>Author personal communication states, "All patients had either one failed antidepressant failure,</p>	<p><i>Subgroups</i> No Subgroups</p> <p><i>Baseline n</i> mITT G1: 92 G2: 98</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: NR G2: NR</p>	<p><i>HAM-D (Insert #)</i> Yes HAMD24 G1:rTMS G2: Sham</p> <p>N Analyzed mITT G1: 92 G2: 98 Observed: G1: 92 G2: 98</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p><i>Research Objective</i> To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder</p> <p><i>Quality Rating</i> Good</p>	<p>rescheduled, missed, or partially completed rTMS sessions dueing weeks 2 to 6) Fully Adherent (fewer than 2 rescheduled, missed, or partially complete sessions; must not have been taking prohibited psychiatric medications or illicit drugs; and had no other protocol violations)</p> <p><i>N</i> Randomized: 199 ITT: 190 Completers: 154 Adherent: 120</p> <p><i>Duration</i> Fixed Duration Active Treatment: 3 wks Variable Duration Active Treatment: 3 wks No-treatment lead-in: 2 wks HAM-D assessment performed twice weekly Acute trial terminated when patients met the stable remission criteria.</p>	<p>or multiple intolerance to antidepressant medications." • Not required in the current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Antidepressant medication-free outpatients; 18-70 yo; DSM-IV MDD, single or recurrent; HAM-D24 ≥ 20; Stable during 2wk medication-free lead-in; moderate level of treatment resistance as defined by the Antidepressant Treatment History Form (ATHF); insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥ 3 trials.</p> <p><i>Exclusion criteria</i> • Other current Axis I disorders; past failure to respond to an adequate trial of ECT; prior treatment with TMS or VNS; personal or close family history or seizure disorder; Neurologic disorder;</p>	<p>Failed 2 or more, % G1: NR G2: NR</p> <p>Current episode failures, mean Mean, median (SD) G1: 1.62, 1 (1.37) G2: 1.41, 1 (0.97)</p> <p>Mean failed trials Mean, median (SD) G1: 3.34, 2 (2.68) G2: 3.28, 3 (2.11)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 100</p> <p>Bipolar I G1: 0 G2: 0</p> <p>Bipolar II G1: 0 G2: 0</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 47.7 G2: 46.5</p> <p><i>Sex, % females</i> G1: 63</p>	<p>Observed Endpoint: G1: 83 G2: 91 Completers: G1: 72 G2: 82 Fully Adherent: G1: 57 G2: 63</p> <p>Endpoint score, mean (SD) Observed G1: 21.61 (9.26) G2: 23.38 (7.43) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -4.23 to 0.10, -0.42, p = 0.06</p> <p>Change, mean (SD) Observed at 3 weeks G1: -4.65 (NR) G2: -3.13 (NR)</p> <p>Responders, n mITT: G1: 14 G2: 5 p = 0.009 OR of responding to rTMS vs. Sham 4.6 (95%CI, 1.47 to 14.42) Completer:</p>	<p>Cognitive impairment, % NR</p> <p>Dizziness, % NR</p> <p>Headache, % G1: 32 G2: 23</p> <p>Insomnia, % G1: 7.6 G2: 10</p> <p>Post op complications, % NR</p> <p>Somnolence, % G1: 5 G2: 4</p> <p>Suicidality, % Suicidality: NR Suicides: G1: 0 G2: 0</p> <p>Additional Comments Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p><i>Interventions</i> rTMS Sham G1: rTMS G2: Sham G1: rTMS G2: Sham G1:rTMS G2: Sham</p> <p><i>Medications Allowed</i> None (2 week washout)</p> <p><i>Strategy</i> Switch strategy</p> <p><i>Parameters</i> G1: Location: Left prefrontal cortex Frequency: 10 Hz Intensity 120% MT Pulses: 10 pulses per second for 4 seconds; 3000 persession Intertrain interval: 26 seconds Length of Session: 37.5 minutes (75 trains) Fixed Active Treatment - Number of sessions: daily weekday sessions (15 sessions) Blinded treatment for improvers - Number of sessions: daily</p>	<p>Ferromagnetic material in body or close to head; pregnancy; taking meds known to lower seizure threshold.</p>	<p>G2: 51</p> <p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Not Specified, %</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 26.3 (5.0) G2: 26.5 (4.8)</p> <p><i>BDI</i> Baseline score, mean (SD)</p>	<p>G1: 10 G2: 4 p = 0.02 Fully Adherent: Overall = 7 p = 0.14</p> <p>Remitters, n No. (95%CI) mITT: G1: 13 (8.5 to 22.7) G2: 5 (2.3 to 11.4) OR (95%CI): 4.18 (1.32 to 13.24) Completers: G1: 10 (7.8 to 23.7) G2: 4 (2.0 to 11.9) OR (95%CI): 4.92 (1.29 to 18.76) Fully Adherent: G1: 6 (5.0 to 21.2) G2: 2 (1.0 to 10.8) OR (95%CI): NS Remitters by Treatment Phase Phase I Fixed(Wks 1-3) G1: 6 G2: 2 Phase I Variable (Wks 4-6) Week 4 Day 2 G1: 2 G2: 0 Week 4 Day 5 G1: 3 G2: 0 Week 5 Day 2</p>	<p>Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NA</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p>weekday sessions for up to another three weeks (total possible sessions = 30) G2: Similar coil as active treatment with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.</p>			<p>G1: 2 G2: 3 Other Response: $\geq 50\%$ decrease in HAM-D score from baseline) Remission: HAM-D score of 3 or less or 2 consecutive Ham-D scores less than 10</p> <p><i>MADRS</i> Yes G1: rTMS G2: Sham</p> <p>Baseline n Observed Baseline G1: 92 G2: 98 Observed End of Phase I G1: 83 G2: 91</p> <p>Baseline score, mean (SD) G1: 29.5 (6.9) G2: 29.8 (6.4)</p> <p>Endpoint score, mean (SD) Observed at 3 weeks G1: 24.59 (11.44) G2: 27.75 (9.06) G1: vs. G2, 95% CI</p>	<p>Predefined No</p> <p>MMSE No</p> <p>Baseline n</p> <p>Baseline score, mean (SD)</p> <p>Endpoint score, mean (SD)</p> <p>Change, mean (SD)</p> <p>Other</p> <p><i>Other</i> Yes Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%):</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective				
				<p>Effect Estimate, Cohen d, p-value: -6.10 to -0.76, -0.51, p = 0.01</p> <p>Change, mean (SD) Observed at 3 weeks G1: -4.89 (NR) G2: -2.06 (NR)</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other NA</p> <p>IDS Yes G1:rTMS G2: Sham[Q60]</p> <p>Baseline n Observed Baseline: G1: 86 G2: 94 Observed at end of Phase I: G1: 78 G2: 88</p> <p>Baseline score, mean (SD)</p>	<p>G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient</p> <p>Adequate information Yes</p> <p><i>Attrition</i> Overall, % All attrition calculations based on mITT 10.5%</p> <p>At end of treatment, % G1: 12 G2: 9</p> <p>At end of followup, % G1: NA G2: NA</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective				
				<p>G1: 41.0 (9.3) G2: 40.1 (9.8) Endpoint score, mean (SD) Observed at 3 weeks G1: 32.56 (15.40) G2: 36.70 (13.91) G1: vs. G2, 95% CI, Cohen d, p-value: -10.04 to -2.62, -0.66, p = 0.001</p> <p>Change, mean (SD) Observed at 3 weeks G1: -8.42(NR) G2: -3.37 (NR)</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other NA</p> <p>CGI-S Yes G1: rTMS G2: Sham</p> <p>Baseline n Observed at baseline: G1: 90 G2: 98 Observed at end of Phase I:</p>	<p>Withdrawals due to efficacy, % G1: NR G2: NR</p> <p>Withdrawals due to adverse events, % G1: 5.4 G2: 0</p> <p>Other</p> <p><i>Adherence/ compliance</i> Adherence Fully Adherent n= 120 G1: n = 57 G2: n = 63</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
				<p>G1: 82 G2: 90 Baseline score, mean (SD) G1: 4.62 (0.70) G2: 4.63 (0.69)</p> <p>Endpoint score, mean (SD) Observed at 3 weeks G1: 3.96 (1.14) G2: 4.30 (0.87) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -0.68 to -0.09, -0.55, p = 0.01</p> <p>Change, mean (SD) Observed at 3 weeks G1: -0.66 (NR) G2: -0.33(NR)</p> <p>Other NA</p>	
<p><i>Author, Year</i></p> <p>Holtzheimer et al., 2004¹⁹</p> <p><i>Country, setting</i> USA, single center, outpatient/inpatient status not clearly stated</p> <p><i>Funding</i></p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 15</p> <p><i>Duration</i> Primary endpoint</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance Not required or not specified to be in 	<p><i>Treatment Failure</i></p> <p>Failed 7 or more, % G1: 85.7 G2: 37.5</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i></p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7)</p> <p>At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No major adverse events at any point in study. Some subjects experienced mild pain withactive rTMS, but treatments were generally well tolerated.</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p>University of Washington</p> <p><i>Research Objective</i> Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable</p> <p><i>Quality Rating</i> Fair</p>	<p>following 2 weeks of treatment and follow up</p> <p>1 week after txt completed</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> All pts discontinued (failed) AD medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5 • Inter-train interval: 30-60 • Pulses per session: 1600 • Total number of sessions: 10 over 2 wks</p> <p>Sham rTMS • Delivered in same anatomical location with identical</p>	<p>current episode</p> <p><i>Tier 1 Inclusion criteria</i> • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18</p> <p><i>Exclusion criteria</i> • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy</p>	<p>G1: 40.4 G2: 45.4</p> <p><i>Sex, % females</i> G1: 57.1 G2: 42.9</p> <p><i>Right handed, %</i> G1: 100 G2: 100</p> <p><i>HAM-D 17</i> Baseline n G1: 7 G2: 8</p> <p>Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)</p>	<p>1 week follow up G1: 18.8 (2.5) G2: 17.6 (2.1) Change, mean (SD) At week 1 G1: 4.7 G2: 2.8</p> <p>At week 2 G1: 8.1 G2: 5.5</p> <p>1 week follow up G1: 3.9 G2: 3.2 All endpoints, <i>P</i> = NS</p> <p>Responders, n (%) At week 1 G1: 0 G2: 0</p> <p>At week 2 G1: 2 (28.6) G2: 1 (12.5) 1 week follow up G1: 0 G2: 0</p> <p><i>BDI</i> Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)</p> <p>At week 2</p>	<p><i>Neuropsychological or executive functioning</i> Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); <i>P</i> < 0.05). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.</p> <p>MMSE NR There were no major adverse events at any point instudy. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p> <p><i>Attrition</i> Overall, % 0 during treatment. 3 (20%) before final assessment at week 3</p> <p>At end of treatment, % 0</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp			<p>G1: 23.9 (2.6) G2: 22.4 (2.4)</p> <p>1 week follow up G1: 23.9 (1.6) G2: 26.4 (1.9)</p> <p>Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1</p> <p>Change, mean (SD) 1 week follow up G1: -5.7 G2: -2.1 Group x time (all points), <i>P</i> = NS</p>	<p>At end of followup, % G1: 28.6 G2: 12.5 Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p> <p><i>Adherence/ compliance</i> Compliance All 15 subjects completed all 10 txt sessions</p>
<p><i>Author, Year</i> Kauffmann et al., 2004²⁰</p> <p><i>Country, setting</i> NR, NR – investigators for the US</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> Assessefficacy of right prefrontal slow repetitive rTMS in TRD pts</p> <p><i>Quality Rating</i></p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 12</p> <p><i>Duration</i> 10 treatments over 2 weeks</p> <p>Primary Outcome: Change in HAM-D/Response after 10 sessions</p> <p><i>Interventions</i></p>	<p><i>TRD definition</i> • 2+ failed AD trials (8+ weeks at adequate doses) • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> Major Depression (DSM-IV) age 18+</p> <p><i>Exclusion criteria</i> Preexisting neurological and/or</p>	<p><i>Treatment Failure</i> Mean failed trials NR:</p> <p><i>Polarity, %</i> 100% Major Depression</p> <p><i>Age, mean yrs</i> Overall 51.7</p> <p><i>Sex, % females</i> Overall 91.7</p> <p><i>HAM-D 21</i> Baseline n G1: 7 G2: 5</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SEM) G1: 11.29 (3.17) G2: 11.80 (1.93)</p> <p>Change, mean (SD) G1: -10.57 G2: -6.31 <i>P</i> = NR (ns)</p> <p>Responders, n G1: 4 (57%) G2: 2 (40%) Response2, n HAM-D21 <10 G1: 4 (57%) G2: 1 (20%)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Additional Comments</i> There were "No AEs reported" "there were no adverse events"</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
Fair	<p>G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> allowed to continue antidepressants but advised to discontinue benzodiazepines & mood stabilizers</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 2 • Length of train (seconds): 60 • Inter-train interval: 180 • Pulses per session: 120 • Total number of sessions: 10 in 10 days</p> <p>Sham • Same as above but coil was held at a 45 degree angle from skull</p>	cardiac diseases	Baseline score, mean (SEM) G1: 21.86 (2.31) G2: 18.20 (2.20)	<p><i>Relapse</i> On follow up most pts in txt group relapsed after 2-3 month, whereas pts in sham group who improved relapsed in 2 weeks</p>	<p>Predefined Yes</p> <p>MMSE NR</p> <p><i>Other</i> Yes "there were no adverse events"</p> <p>Adequate information No</p> <p><i>Attrition</i> Overall, % 0</p> <p>At end of treatment, % NR</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

| Study Citation, Country, Setting Funding, Research Objective |
|--|--|--|--|--|--|
| | | | | | <i>Adherence/ compliance</i>
NR
NR |

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p><i>Author, Year</i> Padberg et al., 1999²¹</p> <p><i>Country, setting</i> Germany, university clinic, patient status not clear</p> <p><i>Funding</i> Magstim Company Ltd. & Micromed Medizin-Elektronik GmbH</p> <p><i>Research Objective</i> Compare antidepressant efficacy and tolerability of fast, slow, and sham rTMS in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 18</p> <p><i>Duration</i> 1 week of active txt Primary outcome: Change in HAM-D after 5 txt sessions</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: High rTMS G2: Low rTMS G3: Sham rTMS</p> <p><i>Medication allowed</i> 83.3% of pts continued on their current [failed] AD medication, others were not on a med and did not start one prior to trial</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS High</p>	<p><i>TRD definition</i> • 2+ failed txt trials of 4+ wks duration including at least one tricyclic • Required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> MDD (DSM IV)</p> <p><i>Exclusion criteria</i> organic brain disorders, contraindications for rTMS</p>	<p><i>Treatment Failure</i></p> <p>Current episode failures, mean G1: 4.0 (2.2) G2: 3.2 (0.8) G3: 3.2 (1.2)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 63.5 G2: 46.7 G3: 43.3</p> <p><i>Sex, % females</i> G1: 33.3 G2: 83.3 G3: 66.7</p> <p><i>Right handed, %</i> G1: 100 G2: 100 G3: 100</p> <p><i>HAM-D 21</i> Baseline n G1: 6 G2: 6 G3: 6</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) G1: 28.5 (9.4) G2: 21.5 (21.5) G3: 23.5 (10.4)</p> <p>Change, mean (SD) G1: -1.7 G2: -5.2 G3: -1.3</p> <p><i>P</i> > 0.05</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p><i>MADRS</i> Endpoint score, mean (SD) graph only</p> <p>Group x time, <i>P</i> < 0.1</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i></p> <p>Headache, % G1: 16.7 G2: 16.7 G3: NR</p> <p>Focal Pain at rTMS site during stimulations: 50%, 33.3%, & 0%. There were no serious AE.</p> <p><i>Neuropsychological or executive functioning</i> Verbal Memory Tests (included 3 learning trials and a consecutive, delayed recall task after distraction): Verbal memory performance improved significantly after fast rTMS Learning 1. <i>P</i> = 0.006 2. NA 3. Fast rTMS improvement <i>P</i> = 0.032, Slow rTMS <i>P</i> = NS, Sham decrease in performance <i>P</i> = 0.09</p> <p><i>MMSE</i> NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 5 • Length of train (seconds): 5 • Inter-train interval: 30 • Pulses per session: 250 • Total number of sessions: 5/wk <p>rTMS Low</p> <ul style="list-style-type: none"> • Frequency (Hz):0.3 • Motor threshold (%): 90 • Number of trains: 10 • Length of train (seconds): 25 • Inter-train interval: NR • Pulses per session: 75 • Total number of sessions: 5/wk <p>Sham:</p> <ul style="list-style-type: none"> • Same as high rTMS except coil angled at 90 degrees with 1 wing resting on skull 		<p>Baseline score, mean (SD)</p> <p>G1: 30.2 (9.5) G2: 26.7 (9.4) G3: 22.2 (8.8)</p> <p><i>MADRS</i></p> <p>Baseline n</p> <p>G1: 6 G2: 6 G3: 6</p> <p>Baseline score, mean (SD)</p> <p>graph only</p>		<p><i>Attrition</i></p> <p>Overall, % NR, "no pts asked for discontinuation of rTMS"</p> <p>At end of treatment, % NR</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i></p> <p>NR - "compliance was excellent"</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p><i>Author, Year</i> Pallanti et al., 2010²² Pallanti</p> <p><i>Country, setting</i> Italy Single Center Outpatient</p> <p><i>Funding</i> Italian Department of Health</p> <p><i>Research Objective</i> Compare unilateral low frequency, sequential bilateral rTMS treatment and sham in pts with TRD under stable pharmacological treatment</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell</p> <p><i>N</i> 60</p> <p><i>Duration</i> Active treatment: 3 wks Primary outcome measure: HAMD measured weekly</p> <p><i>Interventions</i> Unilateral rTMS Bilateral rTMS Sham G1: Bilateral Stimulation G2: Unilateral Stimulation G3: Sham</p> <p><i>Medications Allowed</i> Current [failed] antidepressant regime continued</p> <p><i>Strategy</i> Augment or add-on strategy</p>	<p><i>TRD definition</i> • Failed two or more adequate (6 weeks or more each) treatments. • Not required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Right-handed; ≥ 18 yrs; HAM-D score ≥ 18; ≥ 2 failed AD trials (≥ 6 wk duration); duration ≥ 4mos for current depressive episode; illness duration ≥ 4 yrs.</p> <p><i>Exclusion criteria</i> • Any additional psychiatric comorbidity; rTMS contraindications (metallic implants, foreign bodies, history of seizures); major medical disease; inability or refusal to provide written informed consent.</p>	<p><i>Subgroups</i> No Subgroups</p> <p><i>Baseline n</i> G1: 20 G2: 20 G3: 20</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 100 G2: 100 G3: 100</p> <p>Failed 2 or more, % G1: 100 G2: 100 G3: 100</p> <p>Current episode failures, mean G1: NR G2: NR G3: NR</p> <p>Mean failed trials No. of previous adequate courses of medication failed: mean (SD, 95%CI) G1: 5.90 (1.48, 5.21-6.59) G2: 6.50 (1.48, 5.21-6.59) G3: 5.95 (1.67, 5.72-7.28)</p>	<p><i>HAM-D (Insert #)</i> Yes HAM-D17 G1: Bilateral Stimulation G2: Unilateral Stimulation G3: Sham</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) NR</p> <p>Responders, n HAM-D reduction up to 10% G1: 5 G2: 4 G3: 15 χ^2 19.17, df 6, Sig. = 0.04 HAM-D reduction up to 25% G1: 5 G2: 6 G3: 3 HAM-D reduction up to 50% G1: 6 G2: 3 G3: 0 HAM-D reduction over 50% G1: 4 G2: 7</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> Overall, % G1: NR G2: NR G3: NR</p> <p>Amnesia, % G1: NR G2: NR G3: NR</p> <p>Cardiovascular adverse events, % G1: NR G2: NR G3: NR</p> <p>Cognitive impairment, % Week 0 G1: 25 G2: 20 G3: 35 Week 3 G1: 15 G2: 10 G3: 30</p> <p>Dizziness, % Week 0 G1: 5 G2: 0 G3: 0 Week 3 G1: 0</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p><i>Parameters</i> G1: Bilateral: Location of Stimuli: 1st applied of right DLPFC then left DLPFC Right DLPFC Frequency: 3 140s trains at 1 Hz Intensity: 110% RMT Interval: 30s intertrain interval Total 420 stimuli per session Left DLPFC Frequency: 20 5s trains at 10 Hz Intensity: 100% RMT Interval: 25 s intertrain interval Total 1000 styimuli per session G2: Unilateral: Location of Stimuli: Right DLPFC Frequency: 3 140s trains at 1 Hz Intensity: 110% RMT Interval: 30s intertrain interval Total 420 stimuli per session Sham: Left DLPFC Same length of time as the 420 stimuli per session.</p>		<p><i>Polarity, %</i> Unipolar G1: 100 G2: 100 G3: 100 Bipolar I G1: NR G2: NR G3: NR Bipolar II G1: NR G2: NR G3: NR <i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 47.60 G2: 51.20 G3: 47.85 <i>Sex, % females</i> G1: 55 G2: 60 G3: 60 <i>Race, % white</i> G1: NR G2: NR G3: NR <i>Not Specified, %</i> G1: NR G2: NR G3: NR</p>	<p>G3: 2 NNT (Response) rTMS1 vs. sham 10.00 (95%CI: 3.13 to -8.39) rTMS2 vs. sham 4.00 (95%CI: 2.01 to 328.11) Remitters, n G1: 2 G2: 6 G3: 1 χ^2 5.49, df 2, Sig. = 0.064 NNT (Remission) rTMS1 vs. sham 20.00 (95%CI: 4.71 to -8.89) rTMS2 vs. sham 4.00 (95%CI: 2.12 to 36.23) Other Remission: HAM-D < 8</p>	<p>G2: 0 G3: 0 Headache, % Week 0 G1: 40 G2: 30 G3: 20 Week 3 G1: 5 G2: 5 G3: 5 Insomnia, % G1: NR G2: NR G3: NR Post op complications, % G1: NR G2: NR G3: NR Somnolence, % G1: NR G2: NR G3: NR Suicidality, % G1: NR G2: NR G3: NR Additional Comments Not including previously listed Aes Pain/burning in the scalp:</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective			
	Carried out with the MAGSTIM placebo coil system.		<p><i>Right handed, %</i> G1: 100 G2: 100 G3: 100</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) Score (SD, 95%CI) G1: 28.75 (6.01, 25.93-31.57) G2: 27.95 (5.89, 25.19-30.71) G3: 29.05 (3.54, 27.39-30.71)</p>		<p>Week 0 G1: 50 G2: 40 G3: 15 Week 3 G1: 5 G2: 0 G3: 10 Anxiety Week 0 G1: 20 G2: 15 G3: 15 Week 3 G1: 0 G2: 0 G3: 5 Seizure Episode Week 0 G1: 0 G2: 0 G3: 0 Week 3 G1: 0 G2: 0 G3: 0</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined Collection method not reported</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

| Study Citation, Country, Setting Funding, Research Objective |
|--|--|--|--|--|---|
| | | | | | MMSE
No

Baseline n

Baseline score, mean (SD)

Endpoint score, mean (SD)

Change, mean (SD)

Other

<i>Other</i>
Yes
Not including previously listed Aes
Pain/burning in the scalp:
Week 0
G1: 50
G2: 40
G3: 15
Week 3
G1: 5
G2: 0
G3: 10
Anxiety
Week 0
G1: 20
G2: 15
G3: 15
Week 3
G1: 0
G2: 0
G3: 5
Seizure Episode
Week 0 |

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

| Study Citation, Country, Setting Funding, Research Objective |
|--|--|--|--|--|---|
| | | | | | <p>G1: 0
 G2: 0
 G3: 0
 Week 3
 G1: 0
 G2: 0
 G3: 0</p> <p>Adequate information
 No</p> <p><i>Attrition</i>
 Overall, %
 NR
 Text states, "none left the study due to pain at the stimulation site"</p> <p>At end of treatment, %
 G1: NR
 G2: NR
 G3: NR</p> <p>At end of followup, %
 G1: NR
 G2: NR
 G3: NR</p> <p>Withdrawals due to efficacy, %
 G1: NR
 G2: NR
 G3: NR</p> <p>Withdrawals due to adverse events, %
 G1: 0</p> |

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					<p>G2: 0 G3: 0</p> <p>Text states, "none left the study due to pain at the stimulation site"</p> <p>Other</p> <p><i>Adherence/ compliance</i></p>
<p><i>Author, Year</i> Pascual-Leone et al., 1996²³</p> <p><i>Country, setting</i> Spain, both inpatients and outpatients</p> <p><i>Funding</i> Generalitat Valenciana and Spanish Ministerio de Educacion y Ciencia</p> <p><i>Research Objective</i> To study effects of focal rTMS on depressive symptoms of 17 patients with medication-resistant depression of psychotic subtype.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT, Cross-over trial</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 17</p> <p><i>Duration</i> Primary endpoint after 1 week of treatment. Total study duration 5 months (3 week washout between treatments)</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: High Frequency rTMS G2: High frequency right rTMS (control)</p>	<p><i>TRD definition</i> • At least three episodes of depression that had been resistant to multiple medications despite combinations and high doses</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Right-handed; • Diagnosed with major depression, psychotic subtype (DSM-III-R) • history of relapsing unipolar major depression • Met safety criteria for rTMS • normal neurological and general physical examinations</p> <p><i>Exclusion criteria</i> • History of bipolar</p>	<p><i>Subgroups</i> Psychosis</p> <p><i>Treatment Failure</i> Mean failed trials Overall: NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100</p> <p><i>Age, mean yrs</i> Overall: 48.6</p> <p><i>Sex, % females</i> Overall: 59%</p> <p><i>Right handed, %</i> Overall: 100</p> <p><i>HAM-D 21</i> Baseline n Overall: 17 (cross-over study, all patients received all</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) G1: 13.8 G2: NR G3: NR G4: NR G5: NR</p> <p>Change, mean (SD) G1: -11.4 G2: NR G3: NR G4: NR G5: NR $P < 0.001$</p> <p>G1: vs. All controls, $P < 0.0005$</p> <p><i>BDI</i> Endpoint score, mean (SD) G1: 25.7 G2: NR G3: NR</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: 41% G2:</p> <p>Amnesia, % G1: NR G2:</p> <p>Cardiovascular adverse events, % G1: NR G2:</p> <p>Cognitive impairment, % G1: NR G2:</p> <p>Dizziness, % G1: NR G2:</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p>G3: Sham left rTMS G4: Sham right rTMS G5: Real vertex stimulation (control)</p> <p><i>Medications Allowed</i> Attempts were made to taper medications. Nine patients continued AD medication and only 4 patients were AD free at the end of the study. All pts given nimodipine at a constant dose of 30mg/3x daily</p> <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i></p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 10 • Inter-train interval: 60 • Pulses per session: 2000 • Total number of sessions: 5 in 5days • Left Sham Coil angled at 45 degrees with edge of coil 	<p>disorder</p> <ul style="list-style-type: none"> • History of brain surgery or epilepsy • Concurrent serious medical illnesses requiring long-term treatment; • Previously received rTMS 	<p>interventions)</p> <p>Baseline score, mean (SD) G1: 25.2 G2: NR G3: NR G4: NR G5: NR BDI</p> <p>Baseline score, mean (SD) G1: 47.9 G2: NR G3: NR G4: NR G5: NR</p>	<p>G4: NR G5: NR</p> <p>Change, mean (SD) G1: -22.2 G2: NR G3: NR G4: NR G5: NR $P < 0.0001$ G1: vs. All controls, $P < 0.0005$</p>	<p>Headache, % G1: NR G2:</p> <p>Insomnia, % G1: NR G2:</p> <p>Post op complications, % G1: NR G2:</p> <p>Somnolence, % G1: NR G2:</p> <p>Suicidality, % G1: NR G2:</p> <p>Additional Comments Study does not report how A.E.s were reported or elicited. It does state that all pts tolerated rTMS without complications; No seizure induced. Seven pts complained about minor headaches that were not related to stimulation condition.</p> <p><i>Neuropsychological or executive functioning</i> No</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	resting on scalp • Right Sham Coil angled at 45 degrees with edge of coil resting on scalp				Measures, Results NR Predefined No MMSE NR <i>Other</i> Yes Study does not report how A.E.s were reported or elicited. It does state that all pts tolerated rTMS without complications; No seizure induced. Seven pts complained about minor headaches that were not related tostimulation condition. Adequate information No <i>Attrition</i> Overall, % NR At end of treatment, % G1: NR G2: At end of followup, % G1: NR G2:

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					<p>Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2:</p> <p>Other The authors report, "All patients tolerated rTMS without complications... complications were not related to stimulation condition and did not prompt pts to request discontinuation of study."</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Rush et al., 2005²⁴ Carpenter et al., 2004²⁵</p> <p><i>Country, setting</i> US, multicenter, outpatient psychiatric</p> <p><i>Funding</i> Cyberonics, Inc.</p> <p><i>Research Objective</i> To compare adjunctive VNS to sham in TRD</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> m-ITT/PP for efficacy, ITT for Aes</p> <p><i>N</i> 235</p> <p><i>Duration</i> 10wks of stimulation Primary Outcome: HAM-D Response after</p>	<p><i>TRD definition</i> • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+</p>	<p><i>Treatment Failure</i> Percent with 4-6 current episode failures G1: 46.5% G2: 40.0%</p> <p><i>Polarity, %</i> Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6</p>	<p><i>HAM-D24</i> N analyzed G1: 112 G2: 110</p> <p>Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) P = 0.639 Responders, n G1: 17 (15.2%)</p>	<p><i>Quality of Life</i> Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p>patients</p> <p><i>Quality Rating</i> Good</p>	<p>10wks txt</p> <p>Interventions G1: VNS G2: Sham</p> <p><i>Medications allowed</i> pts allowed up to 5 antidepressants, mood stabilizers, or other psychotropic medications</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> VNS: Frequency (Hz): 20 Pulse width (seconds): 500 μs • On/Off cycle parameters: 30 sec on and 5 min off • Duration of treatment:</p> <p>Sham: • Device implanted but not turned on</p>	<p>MDE in lifetime,</p> <ul style="list-style-type: none"> • age 18-80, HAM-D24\geq20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delirium, dementia, amnesia • other cognitive disorder, suicidality • risks related to surgical implantation 	<p>Bipolar II</p> <p>G1: 6.3 G2: 5.5</p> <p>Age, mean yrs G1: 47.0 G2: 45.9</p> <p>Sex, % females G1: 59 G2: 66</p> <p>Race, % white G1: 97 G2: 96</p> <p><i>HAM-D24</i> Baseline n G1: 119 G2: 116</p> <p>Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2)</p> <p><i>MADRS</i> Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3)</p> <p><i>IDS</i> Baseline n G1: 112 (115 randomized) G2: 110</p> <p>Baseline score, mean (SD) G1: 44.3(9.1)</p>	<p>G2: 11 (10.0%) <i>P</i> = 0.251</p> <p><i>MADRS</i> Endpoint score, mean (SD) NR</p> <p>% change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) <i>P</i> = 0.208</p> <p>Responders, n G1: 17 (15.2) G2: 12 (0.0) <i>P</i> = 0.378</p> <p><i>IDS</i> Endpoint score, mean (SD) NR</p> <p>% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) <i>P</i> = 0.158</p> <p>Responders, n G1: 19 (17) G2: 8 (7.3) <i>P</i> = 0.032</p> <p>Remitters, n NR</p> <p><i>CGI-I</i> Endpoint score, mean (SD) NR</p>	<p>Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6)</p> <p>G2: physical component - 1.6(8.4); mental component: 4.0(10.2)</p> <p>Other Physical component between VNS and sham: <i>P</i> = 0.480, Mental Component between VNS and sham: <i>P</i> = 0.406</p> <p><i>Adverse Events</i> Overall, % NR Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:– • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%,</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective			
			<p>G2: 45.4(8.5)</p> <p><i>CGI-I</i> Baseline n G1: 112 G2: 110</p>	<p>Achieving 1 or 2 score, % (SD) G1: 13.9 G2: 11.8 VNS v. Sham, <i>P</i> = 0.648</p>	<p>• hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0%</p> <p>Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11 patients, were cases of worsening depression requiring hospitalization</p> <p>Cardiac SAEs during implantation: 1.7% v 0% COSTART used to code reported events</p> <p><i>Attrition</i> Overall, % 1.3 (3/235)</p> <p>At end of treatment, % G1: 2.6 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % NR Withdrawals due to adverse events, %</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
					G1: 2.6 G2: 0 9 pts had a protocol violation post randomization <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Su et al., 2005²⁶</p> <p><i>Country, setting</i> Taiwan, NS</p> <p><i>Funding</i> Taipei Veterans General Hospital, patient status not reported</p> <p><i>Research Objective</i> To investigate whether two weeks of rTMS applied to LDLPFC can alleviate TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 33</p> <p><i>Duration</i> 2wk of active txt Primary outcome: HAM-D at 2 weeks (after 10 txt)</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: 20Hz rTMS (N analyzed = 10) G2: 5Hz rTMS (N analyzed = 10) G3: Sham (N analyzed = 10)</p> <p><i>Medications allowed</i> pts allowed to continue</p>	<p><i>TRD definition</i> • TRD (2+ failed adequate trials) • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major Depressive Episode or Bipolar (DSV-IV), • Ham-D21 score >=18</p> <p><i>Exclusion criteria</i> • history of - epilepsy, • any physical and neurological abnormalities, major head trauma, • psychotic symptoms; • current use of a pacemaker, • suicidality</p>	<p><i>Subgroups</i> Ethnicity - Chinese, females by menopausal status</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 90 G2: 80 G3: 80 Bipolar G1: 10 G2: 20 G3: 20 Bipolar II G1: 10 G2: 10 G3: 10 Age, mean yrs G1: 43.6 G2: 43.2 G3: 42.6 Sex, % females G1: 70 G2: 80</p>	<p><i>HAM-D 21</i> N analyzed G1: 10 G2: 10 G3: 10</p> <p>Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 12.3(7.7) G3: 19.0(7.7)</p> <p>Change, mean (SD) At 2 weeks G1: -13.4(4.9) G2: -14.2(6.0) G3: -3.7(9.3) G1: vs. G3, G2 vs. G3 <i>P</i> < 0.01 Responders, n G1: 6 (60) G2: 6 (60) G3: 1 (10) G1: + G2 vs. G3 <i>P</i> = 0.01</p> <p>Remitters, n Ham-D17<= 7</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 20 (n=2) G2: 20 (N=2) G3: 11.1 (N=1) Pain at rTMS site: 16.7% withdrew due to pain at stimulation site SEE AE section</p> <p><i>Attrition</i> Overall, % 9.1 (3/33) At end of treatment, % G1: 0 G2: 16.7 G3: 9.1</p> <p>At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0 G2: 0 G3: 9.1</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	<p>all meds constant for 4 weeks prior (e.g. antidepressants, antipsychotics, mood stabilizers, or stimulant <i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS High:</p> <ul style="list-style-type: none"> • Frequency (Hz): 20 • Motor threshold (%): 100 • Number of trains:40 • Length of train (seconds):2 • Inter-train interval:28 • Pulses per session: 1600 • Total number of sessions: 5/wk or 10 in 10 weekdays <p>rTMS Low:</p> <ul style="list-style-type: none"> • Frequency (Hz): 5 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 8 • Inter-train interval: 22 • Pulses per session: 1600 • Total number of sessions:5/wk or 10 in 10 days 		<p>G3: 70</p> <p>HAM-D 17 Baseline N G1: 10 G2: 12 G3: 11 Baseline score, mean (SD) G1: 23.2 (7.5) G2: 26.5 (5.2) G3: 22.7 (4.7)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.0(9.1) G2: 33.9(7.6) G3: 33.4(9.6)</p> <p><i>CGI-S</i> Baseline score, mean (SD) G1: 4.5(0.7) G2: 4.7(0.8) G3: 4.7(0.48)</p>	<p>G1: 5 (50) G2: 5 (50) G3: 0 <i>BDI</i> Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 19.7(12.3) G3: 28.7(15.1)</p> <p>Change, mean (SD) At 2 weeks G1: 15.2(7.5) G2: 14.2(10.4) G3: 4.7(9.1)</p> <p>G1: vs. G3 $P < 0.05$ G2 vs. G3 $P < 0.1$</p> <p><i>CGI-S</i> Endpoint score, mean (SD) At week 2 G1: 2.8(1.1) G2: 2.0(0.9) G3: 3.6(1.1) Change, mean (SD) G1: -1.7 G2: -2.0 G3: -1.1 $P = NS$</p>	<p>Withdrawals due to adverse events, % G1: 0 G2: 16.7 G3: 0 1 dropped out of sham for worsening of clinical symptoms, this was categorized as LOE <i>Adherence/ compliance</i> NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
	Sham: • Same as high frequency rTMS. Coil placed at 90 degrees off skull.				
<p><i>Author, Year</i> Zheng et al., 2010²⁷</p> <p><i>Country, setting</i> China, Single Center, inpatient/outpatient setting not clearly reported</p> <p><i>Funding</i> National Natural Science Foundation of China (30830046 to Lingjiang Li), the National Science and Technology Program of China (2007BAI17B02 to Lingjiang Li), the National 973 Program of China (2009CB918303, 2007CB512308 to Lingjiang Li and Zhang Zhijun); Program of Chinese Ministry of Education (20090162110011 to Lingjiang Li); National Hi-Tech Research and Development Program</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell</p> <p><i>N</i> 34</p> <p><i>Duration</i> 4 weeks</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> Augment – all patients taking escitalopram from 2+ weeks before trial</p> <p><i>Strategy</i> Augment or add-on strategy</p> <p><i>Parameters</i> rTMS - 20 sessions of rTMS over the left DLPFC within four weeks, at 110% stimulation intensity</p>	<p><i>TRD definition</i> • failure to respond to at least two different antidepressants given for a period longer than 4 weeks at the maximum recommended dose. • Not required to be in current episode</p> <p><i>Tier -1</i></p> <p><i>Inclusion criteria</i> • Fulfilling the diagnostic criteria for major depressive episode (DSM-IV) and referred for rTMS because of drugtreatment resistance were enrolled in this study. • Age of the patients was from 18 to 37 years</p> <p><i>Exclusion criteria</i> • Any other psychiatric axis-I or axis-II disorders</p>	<p><i>Subgroups</i> Young adults (18-37)</p> <p><i>Baseline n</i> G1: 19 G2: 15</p> <p><i>Treatment Failure</i> Failed 1 or more, % 100</p> <p>Failed 2 or more, % 100</p> <p>Current episode failures, mean NR</p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 26.9 G2: 26.7</p> <p><i>Sex, % females</i></p>	<p><i>HAM-D (17)</i> Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 22.9 (3.4) Change, mean (SD) G1: -11.1 G2: -1.7 <i>P</i> = NR</p> <p>Responders, n G1: 12 G2: 1</p> <p>Remitters, n NR</p> <p>Other Responders - Fisher's exact test, <i>P</i> < 0.001</p> <p><i>BDI</i> Yes G1: rTMS G2: Sham</p> <p>Endpoint score, mean (SD) G1: 13.5 (5.1) G2: 19.8 (5.1)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> NR</p> <p><i>MMSE</i> NR</p> <p><i>Other</i> NR</p> <p><i>Attrition</i> NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 4. KQ1 active versus control: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective	Study Citation, Country, setting Funding, Research Objective
<p>of China (863 program: 2008AA02Z413 to Zhang Zhijun)</p> <p><i>Research Objective</i> To assess metabolic changes within prefrontal cortex after rTMS treatment</p> <p><i>Quality Rating</i> Fair</p>	<p>related to resting motor threshold</p>	<ul style="list-style-type: none"> • History of epileptic seizures or any other neurological disorder • Any kind of metal implants • Any other clinically relevant abnormalities in their medical history or laboratory examinations • Medical history of alcohol or drug abuse 	<p>G1: 36.8 G2: 33.3</p> <p><i>Race, % white</i> NR</p> <p><i>Not Specified, %</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 24.6 (3.0) G2: 24.6 (2.8)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 21.1 (4.2) G2: 21.0 (4.2)</p>	<p>Change, mean (SD) G1: -7.6 G2: -1.2</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	

Evidence Table 5. KQ1 active versus control: Tier 2

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Berman et al., 2000²⁸</p> <p><i>Country, setting</i> US, urban community health center, inpatient and outpatients</p> <p><i>Funding</i> Veterans Administration, NIMH, State of CT</p> <p><i>Research Objective</i> To assess efficacy of rTMS in unmedicated TRD patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> 2 weeks (10 weekdays of txt)</p> <p><i>Primary outcome = Interventions</i> G1: rTMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imipramine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Current Major depressive episode (via Ham-D)</p> <p><i>Exclusion criteria</i> • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control</p>	<p><i>Treatment Failure</i> Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 Age, mean yrs G1: 45.2 G2: 39.4 Sex, % females G1: 20 G2: 40 Race, % white G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic)</p> <p><i>HAM-D 25</i> Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 37.1 G2: 37.3</p>	<p><i>HAM-D 25</i> G1: rTMS G2: Sham TMS</p> <p>Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) <i>P</i> < 0.01</p> <p>Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 <i>P</i> = 0.09 Three partial responders returned to baseline within 1-2 weeks</p> <p><i>BDI</i> Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) <i>P</i> = 0.27</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, n G1: 60 G2: 50</p> <p>Difficulty starting urination great in active group <i>P</i> = 0.03</p> <p>Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR)</p> <p>Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appétit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days <p>Sham</p> <ul style="list-style-type: none"> • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp 				<p>coordination, and muscle stiffness</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Manes et al., 2001²⁹</p> <p>Includes additional neuro-psychological outcomes reported in Moser et al., 2002³⁰</p> <p><i>Country, setting</i> US, outpatient clinic</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> cannot tell if ITT</p> <p><i>N</i> 20</p>	<p><i>TRD definition</i> • Not required or not specified to be in current episode</p> <p><i>Setting(s)</i> Outpatient Psychiatric</p>	<p><i>Subgroups</i> Age 50+</p> <p><i>Treatment Failure</i> Mean failed trials G1: 4 (2.3) G2: 4 (1.2)</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) At 1 week G1: 13.7 (5.4) G2: 16.2 (8.5) 1 week Follow-up G1: 14.4 (6.4) G2: 15.5 (9.1)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 40% G2: 0% Other:</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To examine antidepressant efficacy of rTMS in a TRD population</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Duration</i> 2 weeks (1 week of treatment, 1 wk follow-up following last treatment)</p> <p>Primary outcomes HAM-D at end of treatment and at 1 week follow-up</p> <p><i>Interventions</i> G1: rTMS (N=10) G2: Sham rTMS (N=10)</p> <p><i>Medications allowed</i> No antidepressant medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk 	<p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Major/Minor Depression (DSM IV), • TRD (1+ failed trial) <p><i>Exclusion criteria</i> NR</p>	<p><i>Polarity, %</i> Major Depression G1: 80 G2: 100</p> <p>Dysthymia G1: 20 G2: 0</p> <p>Age, mean yrs G1: 60.5 G2: 60.9</p> <p>Sex, % females G1: 50 G2: 50</p> <p>Race, % white G1: 100 G2: 100</p> <p><i>HAM-D</i> Baseline n G1: 10 G2: 10</p> <p>Baseline score, mean (SD) G1: 22.7 (5.2) G2: 22.7 (7.1)</p>	<p>Change, mean (SD) At week 1 G1: -9 G2: -6.5</p> <p>1 week follow-up G1: -8.3 G2: -7.2</p> <p>All time points $P > 0.66$; pts with MDD only - $P = 0.3919$</p> <p>Responders, n (%) G1: 3 (30) G2: 3 (30)</p> <p>$P = NS$</p> <p>Remitters, n G1: 2 G2: 2 $P = NR$</p>	<p>Local pain/local discomfort: 10%/40% vs. 0%/40%; anxiety: 0 vs 10%</p> <p><i>Neuropsychological or executive functioning</i> **30 (endpoint: mean of 3 days after 5 days of txt)</p> <p>Trail Making Test B score Baseline: rTMS: 87.22 Sham: 103.67</p> <p>Follow-up rTMS: 58.59 Sham: 100.64</p> <p>**some variation in pts included in two samples but reported as same study by authors. #1564 includes at least 1 participant <50 years old, n=19</p> <p>Other neuropsychological tests showing no statistical significance in either group: Trail Making Test-A, Stroop Test, WAIS-R digit symbol, Controlled Oral Word Association, Boston naming test,</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham: • Same stimulation, figure 8 coil was above top of skull and handle was placed against head				stentance repetition, Rey Auditory Verbal Learning test, & Judgement of Line Orientation <i>MMSE</i> Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 28.7 (1.4) G2: 28.6 (1.3) Endpoint score, mean (SD) At Week 1 G1: 29.6(0.7) G2: 29.3 (0.7) At Follow-up Week 1 G1: 29.6(1.8) G2: 29.2 (0.8) Change, mean (SD) NR 1. <i>P</i> >0.41 2. <i>P</i> = NA 3. <i>P</i> = NR <i>Attrition</i> NR <i>Adherence/ compliance</i> NR

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> O'Reardon, 2007³¹</p> <p><i>Country, setting</i> US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported</p> <p><i>Funding</i> Neuronetics</p> <p><i>Research Objective</i> To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral perfrontal cortex is effective and safe in acute treatment of major depression</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 325 randomized</p> <p><i>Duration</i> 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over after 4 weeks if not responding.</p> <p><i>Interventions</i> G1: Active TMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use of hypnotics, anxiolytics for tx emergent insomnia or anxiety</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 10</p>	<p><i>TRD definition</i> • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime</p> <p><i>Tier 2 Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i> • Aged 18–70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed at screening assessment</p> <p><i>Exclusion criteria</i> • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder • Posttraumatic stress disorder and eating disorders (if present in past year)</p>	<p><i>Baseline N</i> G1: 165 G2: 160 Current episode failures, mean G1: 1.6 G2: 1.6</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar 100</p> <p>Age, mean yrs G1: 47.9 G2: 48.7</p> <p>Sex, % females G1: 55.5% G2: 50.7%</p> <p>Race, % white G1: 94.2% G2: 89.7%</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 22.6 (3.3) G2: 22.9 (3.5)</p> <p><i>MADRS</i> Baseline n G1: 155 G2: 146</p>	<p><i>HAM-D 17</i> Analyzed n G1: 155 G2: 146</p> <p>Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5) At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0)</p> <p>Change, mean (SD) At week 2 G1: -5.2 G2: -3.5 At week 6 G1: -5.5 G2: -3.3 P = 0.005</p> <p>Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9)</p> <p>P > 0.10 At week 4 G1: 32 (20.6) G2: 17 (11.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Serious adverse events G1: 6 G2: 5 Suicidality, % G1: 0.6 G2: 1.9 • Exacerbation of depression: active TMS = 0.6%, sham TMS = 1.9% • Eye pain: active TMS = 6.1% sham TMS = 1.9%; • GI disorders toothache: active TMS = 7.3%, sham TMS = 0.6%; • Application site discomfort: TMS = 10.9%, sham = 1.3% • Application site pain, %: TMS = 35.8, sham = 3.8 • Facial pain: active TMS = 6.7%, sham TMS = 3.2 • Muscle twitching: TMS = 20.6%, sham = 3.2% • Pain of skin: TMS = 8.5%, TMS = 0.6%</p> <p><i>MMSE</i> NR</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks <p>rTMS Sham:</p> <ul style="list-style-type: none"> • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil 	<ul style="list-style-type: none"> • Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head 	<p>Baseline score, mean (SD)</p> <p>G1: 32.8 (6.0) G2: 33.9 (5.7)</p> <p><i>IDS</i></p> <p>Baseline n</p> <p>G1: 155 G2: 146</p> <p>Baseline score, mean (SD)</p> <p>G1: 42.0 (9.4) G2: 43.4 (9.9)</p> <p><i>CGI-S</i></p> <p>Baseline n</p> <p>G1: 155 G2: 146</p> <p>Baseline score, mean (SD)</p> <p>G1: 4.7 (.6) G2: 4.7 (.7)</p>	<p>$P < 0.05$</p> <p>At week 6</p> <p>G1: 38 (24.5) G2: 20 (13.7)</p> <p>$P < 0.05$</p> <p>Remission rate n (%)</p> <p>HAM-D17 < 8</p> <p>At week 2</p> <p>G1: 5 (3.2) G2: 3 (2.1)</p> <p>$P > 0.10$</p> <p>At week 4</p> <p>G1: 110 (7.1) G2: 9 (6.2)</p> <p>$P > 0.10$</p> <p>At week 6</p> <p>G1: 24 (15.5) G2: 13 (8.9)</p> <p>$P = 0.065$</p> <p><i>MADRS</i></p> <p>Endpoint score, mean (SD)</p> <p>At 4 weeks</p> <p>G1: 27 (11.1) G2: 29.8 (10.1)</p> <p>At 6 weeks</p> <p>G1: 26.8 (12.8) G2: 30 (10.8)</p> <p>Change, mean (SD)</p> <p>At 4 weeks</p> <p>G1: 5.8 G2: 4.1</p>	<p><i>Attrition</i></p> <p>Overall, %</p> <p>15</p> <p>At end of treatment, %</p> <p>G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6%</p> <p>At end of follow-up, %</p> <p>G1: NR G2: NR</p> <p>Withdrawals due to efficacy, %</p> <p>G1: 0.6% G2: 1%</p> <p>Withdrawals due to adverse events, %</p> <p>G1: 5% G2: 4%</p> <p>Other</p> <ul style="list-style-type: none"> • 325 subjects were randomized • 24 were "nonevaluable" • 301 continued to receive at least 1 treatment, these 301 were included in final analysis • 277 completed study through week 4. <p><i>Adherence/ compliance</i></p> <p>NR</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At 6 weeks G1: 6 G2: 3.9</p> <p>Response rate, % At week 2 G1: 8.4 G2: 6.2</p> <p><i>P</i> > 0.10 At week 4 G1: 18.1 G2: 11.0</p> <p><i>P</i> < 0.05 At week 6 G1: 23.9 G2: 12.3 <i>P</i> < 0.01</p> <p>Remission rate, %</p> <p>Remission defined as total score < 10 At week 2 G1: 3.9 G2: 2.1</p> <p><i>P</i> > 0.10 At week 4 G1: 7.1 G2: 6.2</p> <p><i>P</i> > 0.10 At week 6 G1: 14.2 G2: 5.5 <i>P</i> < 0.05</p>	

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Stern et al., 2007³²</p> <p><i>Country, setting</i> NR, outpatient setting</p> <p><i>Funding</i> The Milton Fund, NARSAD, Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Ciencia</p> <p><i>Research Objective</i> To test hypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in the analysis</p> <p><i>N</i> 45</p> <p><i>Duration</i> • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse.</p> <p>Primary Outcome: HAM-D at 2 weeks and 2 weeks after treatment</p> <p><i>Interventions</i> G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz rTMS to right DLPFC G4: Sham rTMS</p> <p><i>Medications allowed</i> No psychotropic medications were allowed</p> <p><i>Parameters</i> rTMS</p>	<p><i>TRD definition</i> • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score \geq 20</p> <p><i>Exclusion criteria</i> • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100 % MDD</p> <p>Age, mean yrs G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3</p> <p>Sex, % females G1: 60 G2: 60 G3: 70 G4: 60</p> <p><i>Right handed, %</i> 100</p> <p><i>HAM-D 21</i> Baseline n G1: 10 G2: 10 G3: 10 G4: 15</p> <p>Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)</p>	<p><i>HAM-D 21</i></p> <p>Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1)</p> <p>G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6)</p> <p>Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3)</p> <p>Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3)</p> <p>Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7</p> <p>% change, $P = 0.001$ 2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> 9/45 pts reported severe headaches (pts by group NR); no seizures</p> <p><i>Attrition</i> Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20</p> <p>Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period. Reported in text as dropped out following week 2.</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>High Frequency:</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days <p>Low Frequency LDLPFC:</p> <ul style="list-style-type: none"> • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days <p>Low Frequency RDLPFC:</p> <ul style="list-style-type: none"> • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 	<ul style="list-style-type: none"> • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy 		<p>% change, $P = 0.00001$</p> <p>Responders, n</p> <p>At week 1</p> <p>G1: 0</p> <p>G2: 0</p> <p>G3: 0</p> <p>G4: 0</p> <p>At week 2</p> <p>G1: 5 (50%)</p> <p>G2: 0 (0%)</p> <p>G3: 5 (50%)</p> <p>G4: 0 (0%)</p> <p>G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$)</p> <p>1 week follow-up</p> <p>G1: 6 (60%)</p> <p>G2: 0 (0%)</p> <p>G3: 6 (60%)</p> <p>G4: 0 (0%)</p> <p>G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$)</p> <p>2 week follow-up</p> <p>G1: 4 (40%)</p> <p>G2: 0 (0%)</p> <p>G3: 6 (6%)</p> <p>G4: 0</p> <p>G1: > G2 + G4 and G3 > G2 + G4, ($P < 0.0005$)</p> <p>Remitters, n</p> <p>HAM-D \leq 10</p> <p>At week 1</p> <p>G1: 0 (0%)</p> <p>G2: 0 (0%)</p> <p>G3: 0 (0%)</p>	<p><i>Adherence/ compliance</i></p> <p>NR</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Total number of sessions: 10 days <p>Sham rTMS:</p> <ul style="list-style-type: none"> Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above <p><i>Strategy</i> Switch</p>			<p>G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 <i>P</i> = NS (all times); G2 vs. G4 and G1: vs. G3 <i>P</i> = NS (all times)</p>	
<p><i>Author, Year</i> Wiles et al., 2008³³</p> <p><i>Country, setting</i> Bristol, UK, 3 general primary care practices, outpatient setting</p> <p><i>Funding</i> NHS</p> <p><i>Research Objective</i> In TRD, can you feasibly compare CBT + CM vs.</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 25</p> <p><i>Duration</i> 4 months</p>	<p><i>TRD definition</i> • All patients had BDI 15 or more and had complied with an adequate medication</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • 18-65 years; • BDI II score ≥ 15 • have complied with their antidepressant medication</p>	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100</p>	<p><i>BDI</i> Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) CBT+CM scores decreased by an average of 11.2 points more than CM alone (95%CI -19.3-3.1)</p>	<p><i>Quality of Life</i> Scale NR</p> <p>Baseline n NR</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>CM in primary care (pilot study); primary outcome at 4 months</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Interventions</i> G1: CBT + clinical management G2: Usual Care (clinical management)</p> <p><i>Medications allowed</i> No restrictions</p> <p><i>Strategy</i> Unlimited</p> <p><i>Parameters</i> • Type of therapy: CBT • Method: NR • Number of sessions/week: NR • Total number of sessions: 12-20. • Usual care (no restrictions)</p>	<ul style="list-style-type: none"> • Met ICD-10 criteria for depression <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Bipolar disorder, psychosis, personality disorder or major alcohol or substance abuse problems; • Those who had been continually depressed for more than 5 years; • Those unable to complete study questionnaires; • Previous CBT • Those currently receiving other psychotherapy or secondary care for their depression 	<p><i>BDI</i> Baseline n G1: 14 G2: 11</p> <p>Baseline score, mean (SD) G1: 31.1 (8.5) G2: 26.8 (6.8)</p>	<p>Responders, n (%) G1: 8 (57.1) G2: 0 <i>P</i> = NR</p> <p>Remitters, n NR</p>	<p>Change, mean (SD) NR</p> <p>There were no differences between groups in QOL at 4mos. (data NR)</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined NA - No AE data reported</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 8%</p> <p>At end of treatment, % G1: 0 G2: 18.2</p> <p>At end of followup, % G1: 0 G2: 18.2</p>

Evidence Table 5. KQ1 active versus control: Tier 2 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p> <p><i>Adherence/ compliance</i> Compliance CBT patients could receive 12-20 sessions. AT 4 mos, median = 9.5 [IQR: 2, 12]. Patients attending <5 sessions (35.7%), patients attending 5-9 sessions (14.3%), patients attending >=10 sessions (50%).</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Bortolomasi et al., 2006³⁴</p> <p><i>Country, setting</i> Italy, single center, inpatient vs. outpatient NR</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To investigate outcome of depressed patients treated for 1 month with high frequency rTMS on left frontal lobe at long time periods</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in analysis</p> <p><i>N</i> 19</p> <p><i>Duration</i> Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article</p> <p>Interventions G1: rTMS G2: Sham</p> <p><i>Medications allowed</i> Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry)</p> <p><i>Strategy</i> Augmentation Allowed to continue on failed SSRIs (63.2%) and TCAs (26.3%),</p>	<p><i>TRD definition</i> • Drug resistance (not defined) • Not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations</p> <p><i>Exclusion criteria</i> • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 83.3 G2: 85.7</p> <p>Bipolar G1: 16.7 G2: 14.3</p> <p>Age, mean yrs G1: range 45-56 G2: range 44-53 Overall: 55.6</p> <p>Sex, % females G1: 58 G2: 57</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> Overall: 100</p> <p>Groups similar at baseline Yes</p> <p><i>Tier</i></p> <p><i>HAM-D 24</i> Baseline n G1: 12 G2: 7</p>	<p><i>HAM-D 24</i></p> <p>Endpoint score, mean (SD) At week 1 G1: 11.33 G2: 18.29 At week 4 G1: 11.42 G2: 19.14</p> <p>At week 12 NR</p> <p>Change, mean (SD) At week 1 G1: -13.84 G2: NR P = NR, significant</p> <p>Group x time at wk 2 and 4, P < 0.05 At week 4 G1: -13.75 G2: NR</p> <p>At week 12 NR IG1: rTMS G2: Sham Baseline n G1: 12 G2: 7</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No adverse effects were reported in either group, except for mild cephalgia by three patients treated with anti-inflammatory drugs</p> <p>Headache, % 3 patients reported mild headaches after treatment All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep. 3 patients reported mild headaches after treatment</p> <p><i>Attrition</i></p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>No meds (5.3%)</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil <p>Sham</p> <ul style="list-style-type: none"> • Stimulation coil was placed perpendicular to the scalp surface without direct contact. Coil position was fixed for all TMS sessions, and stimulation at this site evoked minimal motor activity 		<p>Baseline score, mean (SD)</p> <p>G1: 25.17 G2: NR</p>	<p>Baseline score, mean (SD)</p> <p>G1: 25.42 G2: NR</p> <p>Endpoint score, mean (SD)</p> <p>At week 1 G1: 12.25</p> <p>G2: 22.43 At week 4 G1: 11.67 G2: 24.57</p> <p>Change, mean (SD)</p> <p>At week 1 G1: 13.17 G2: NR At week 4 G1: 13.75 G2: NR</p>	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> George et al., 1997³⁵</p> <p><i>Country, setting</i> USA, outpatient setting</p> <p><i>Funding</i> NARSAD, Ted and Vada Stanley Foundation</p> <p><i>Research Objective</i> To test hypothesis: daily left prefrontal rTMS has antidepressant effects</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT, crossover</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 12</p> <p><i>Duration</i> 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt Interventions G1: rTMS G2: sham stimulation</p> <p><i>Medications Allowed</i> ADs tapered for 9, 3 partial responders continued their medication</p> <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • DSM-IV criteria for current MDD • right-handed</p> <p><i>Exclusion criteria</i> • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma</p>	<p><i>Treatment Failure</i></p> <p>Number of previous AD medications Overall: 13.4</p> <p><i>Polarity, %</i> Unipolar Overall: 91.7</p> <p>Bipolar II Overall: 8.3</p> <p><i>Age, mean yrs</i> Overall: 41.8 (12.4)</p> <p><i>Sex, % females</i> Overall: 91.7</p> <p><i>Right handed, %</i> Overall: 100</p> <p><i>HAM-D 21</i> Baseline n G1: 12 G2: 12</p> <p>Baseline score, mean (SD) Overall: 28.5 (4.2)</p>	<p>HAM-D 21 G1: rTMS G2: sham stimulation</p> <p>Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 <i>P</i> < 0.03</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 4/12 G2: NR Suicidality, % G1: 0 G2: Sham: 1/12</p> <p>Seizures: None</p> <p>Unexpected side effects: None</p> <p>Headaches NR by active v. sham</p> <p>Memory or Attention: None</p> <p><i>Attrition</i> Overall: 0</p> <p><i>Adherence/ compliance</i> N</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: NR • Pulses per session: • Total number of sessions: 5/wk for a total of 20 per patient Sham: <ul style="list-style-type: none"> • Same as above but angled at 45 degrees from skull 				
<p><i>Author, Year</i> Harley, 2008³⁶</p> <p><i>Country, setting</i> United States, university clinics, outpatient psychiatric</p> <p><i>Funding</i> Kaplan Fellowship Award Grant through Harvard Medical School</p> <p><i>Research Objective</i> To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 24</p> <p><i>Duration</i> Primary outcome after 16 weeks of active txt Follow-up: 6 months</p> <p><i>Interventions</i> G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control</p> <p><i>Medications Allowed</i> Patients continued antidepressant therapy</p> <p><i>Strategy</i> Augmentation</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • 1+ failed medications (6+ weeks at “standard effective dose”) • Not required or not specified to be in current episode <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabilized on an adequate dose of antidepressant medication before entering study. 	<p>Baseline N G1: 13 G2: 11</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, % MDD</i> <i>Overall:</i> 100</p> <p><i>Age, mean yrs</i> <i>Overall:</i> 41.8</p> <p><i>Sex, % females</i> <i>Overall:</i> 75</p> <p><i>Race, % white</i> <i>Overall:</i> 83</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 16.15 (4.47)</p>	<p><i>HAM-D 17</i> Analyzed n G1: 10 G2: 9</p> <p>Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23)</p> <p>Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78</p> <p><i>P < 0.05 Remitters, n</i> Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) <i>P = NR</i></p>	<p><i>Quality of Life Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT)</i> Baseline n G1: 10 G2: 9 Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24) Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69) Change, mean (SD) G1: -1.3 G2: -0.33 <i>P = NS</i> <i>Social Adjustment Scale-Self-Report (SAS-SR) work subscale</i> Baseline n G1: 10 G2: 9</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <ul style="list-style-type: none"> • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1 • Total number of sessions:16 G2: Wait list 	<p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Borderline personality disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder. • Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience. 	<p>G2: 18.64 (4.72) P = NS</p> <p><i>BDI</i></p> <p>Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) P = NS</p>	<p><i>BDI</i></p> <p>Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30) Change, mean (SD) G1: -12.80 G2: -1.55 P < 0.01</p>	<p>Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95) Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 P < 0.05</p> <p><i>Adverse Events</i> NR</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, %: 21 At end of treatment, % G1:23 G2:18 At end of follow-up, % G1:20 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p> <p>Other 5 participants (3 groups,</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem prevented second from continuing.</p> <p><i>Adherence/ compliance</i> Compliance Participants completed a weekly check-in form asking about medication compliance overpreceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had forgotten a medication dose between 1 to 4 times in previous month.</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Moller, 2006³⁷</p> <p><i>Country, setting</i> Iceland, hospital, inpatient and outpatient</p> <p><i>Funding</i> Government or non-profit organization: Helga Jondottir and Sigurlioi Kristjansson Memorial Fund and Landspítali-University Hospital of Iceland Research Fund</p> <p><i>Research Objective</i> To evaluate antidepressant efficacy of 5 days of left prefrontal rTMS.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT, crossover</p> <p><i>Type of analysis</i> Cannot tell if ITT, all reported patients included</p> <p><i>N</i> 10</p> <p><i>Duration</i> Primary endpoint was within one week of completing txt Interventions G1: rTMS G2: Sham</p> <p><i>Medications allowed</i> Pts continued (failed) AD medication and were allowed benzodiazepines</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 5</p>	<p><i>TRD definition</i> • TRD not defined • Not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Specific inclusion criteria are not reported. • None of pts received rTMS prior. All met safety criteria.</p> <p><i>Exclusion criteria</i> NR</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 80</p> <p>Bipolar Overall: 20%</p> <p><i>Age, mean yrs</i> Overall: 54 (14)</p> <p><i>Sex, % females</i> Overall: 60%</p> <p>HAM-D 17 Baseline n G1: 7 G2: 3 Baseline score, median (range) G1: 20 (13 - 37) G2: 16 (7 - 31)</p>	<p>HAM-D 17 G1: rTMS G2: sham rTMS Endpoint score, median (range) G1: 13 (3 - 27) G2: 15 (4 - 25) Change, median-median G1: -7 G2: -1 P = 0.075</p>	<p><i>Quality of Life</i> NR</p> <p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: 30% G2: 0</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p> <p>Cognitive impairment, % NR</p> <p>Dizziness, % NR Headache, % G1: 20%; 10% Migraine G2:</p> <p>Insomnia, % NR</p> <p>Post op complications, % NR</p> <p>Somnolence, % NR</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: 25 • Pulses per session: 2000 • Total number of sessions: 5 in 5 days <p>Sham</p> <ul style="list-style-type: none"> • Stimulation was over the occipital cortex (stimulator angled 45° with both wings touching the skull) • Augment or add-on strategy 				<p>Suicidality, % NR</p> <p>Additional Comments Only reported on headaches and one migraine. authors do not elaborate on how A.E.s were elicited from pts. Simply, they state, "The magnetic stimulation was well tolerated."</p> <p><i>Neuropsychological or executive functioning</i> Yes; I don't know if P300 fits in with neuropsychological testing but I've extracted all of data from it in following column</p> <p>Measures, Results P300 amplitude, n = 9; One pt could not relax and altered outcomes.</p> <p>The median entry P300 amplitude for patients was 5.7 mV (range 1.0 - 9.5 mV) and latency was 335 ms (range 238 - 370). P300 amplitude changed from 5.7 mV (range 3.2 - 9.5) to 8.1 mV (range 3.3 - 11.6) after left prefrontal stimulation and after</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>sham stimulation from 7.0 mV (range 1.0 - 13.4) to 8.0 (range 2.2 - 12.3). Comparison of changes inP300 amplitude (left prefrontal-group vs. sham-group) shows a significant difference (n = 9, Z = 2.0, P = 0.02). No significant changes were observed inP300 latency.counting performance did not show any difference before and after treatment.</p> <p>Predefined No</p> <p><i>MMSE</i> NR</p> <p><i>Other</i> Only reported on headaches and one migraine. authors do not elaborate on how A.E.s were elicited from pts. Simply, they state, "The magnetic stimulation was well tolerated."</p> <p>Adequate information No</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Attrition</i> Overall, % NR At end of treatment, % G1: NR G2: At end of follow-up, % G1: NR G2: Withdrawals due to efficacy, % G1: NR G2: Withdrawals due to adverse events, % G1: NR G2:</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Paykel, 1999³⁸ Scott, 2000³⁹</p> <p>Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219.</p> <p><i>Country, setting</i> UK, outpatient</p> <p><i>Funding</i> Medical Research Council, London, England and a grant</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 158</p> <p><i>Duration</i> Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68</p>	<p><i>TRD definition</i> • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily</p>	<p><i>Treatment Failure</i> Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar 100% 100% Age, mean yrs G1: 43.2 (11.2) G2: 43.5 (9.8) Sex, % females G1: 53% G2: 46%</p>	<p>HAM-D 17 G1: Clinical Management only G2: CT plus Clinical Management</p> <p>Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2) Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7) Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 20% did not adhere to protocol through to study end or relapse point At end of treatment, % G1: 4 G2: 14</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>from Oxford and Anglia Region</p> <p><i>Research Objective</i> To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintenance treatment with antidepressants.</p> <p><i>Quality Rating</i> Good</p>	<p>wks. Interventions G1: Clinical management Only G2: CT plus Clinical Management</p> <p><i>Medications allowed</i> Continued on current medications with dose adjustments allowed</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> Psychotherapy: • Type of therapy: Cognitive Therapy</p> <p>• Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16</p>	<p>dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months. • Failure required to be in the current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Unipolar depression, • aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression within last 18 months but not in last 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose.</p>	<p><i>HAM-D 17</i> Baseline n G1: 78 G2: 80 Baseline score, mean (SD) G1: 12.1(2.7) G2: 12.2 (2.9) P < 0.05</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)</p>	<p>Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 P = NS Follow-up at 44 weeks G1: -3.0 G2: -4.5 Follow-up at 68 weeks G1: -5.0 G2: -4.9</p> <p>Responders, n NR</p> <p>Remitters, n (%)</p> <p>HAM-D < 8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45))</p> <p><i>BDI</i> Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6), Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3) Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7)</p>	<p>At end of follow-up, % G1: 12 G2: 10</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, • any other primary Axis I disorder attime ofindex illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions. 		<p>Change, mean (SD) At week 20 G1: -6.24 G2: -8.44</p> <p>Responders, n NR</p> <p>Remitters, n</p> <p>BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%)</p> <p>Relapse n(%): At week 20: G1: 18 (23)</p> <p>G2: 10 (13) At week 44 G1: 40 (51)</p> <p>G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36)</p> <p>Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT</p> <p>Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative</p>	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93). Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219: Relapse was defined as: (1) meetingDSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms duringfollow-up phase between 2 successive ratings 2 months apart, reaching a score onHAM-D 17 of at least 13 on both occasions and a level of distress or dysfunction for which the withholding of</p>	

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				additional active treatment was no longer justified.	
<p><i>Author, Year</i> West, 1981⁴⁰</p> <p><i>Country, setting</i> UK, Hospital, inpatient</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> The therapeutic effect of simulated and real bilateral electric convulsion therapy</p> <p><i>Quality Rating</i> KQ1 - Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers or per protocol (PP)</p> <p><i>N</i> 25 (22 analysed)</p> <p><i>Duration</i> 3 weeks</p> <p><i>Interventions</i> G1: ECT G2: Simulated ECT</p> <p><i>Medications Allowed</i> 50 mg amitriptyline</p> <p><i>Strategy</i> Combination</p> <p><i>Parameters</i> The anaesthetic agent was Althesin (alphadolone) and the muscle relaxant suxamethonium. Electric convulsion therapy was administered from a Transycon machine using 40 joules with double-sided unrectified</p>	<p>TRD definition • Referred for ECT</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Primary depressive illness</p> <p><i>Exclusion criteria</i> • NR</p>	<p><i>Subgroups</i> NR</p> <p><i>Baseline n</i> G1: 13 G2: 12</p> <p><i>Treatment Failure</i> NR</p> <p><i>Polarity, %</i> NR</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 52.0 G2: 53.3</p> <p><i>Sex, % females</i> G1: 45 G2: 36</p> <p><i>Race, % white</i> NR</p> <p><i>Not Specified, %</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes</p>	<p><i>N Analyzed</i> G1: 11 G2: 11</p> <p><i>BDI</i> Yes G1: ECT G2: Simulated ECT</p> <p>Endpoint score, mean (SD) G1: 10.8 (SEM 2.6) G2: 22.2 (3.8) <i>P</i> < 0.002</p> <p>Change, mean (SD) G1: -15.8 G2: -1.9</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p><i>Measures, Results</i> None reported</p> <p><i>Predefined</i> NA - No AE data reported</p> <p><i>Adequate information</i> NA - No AE data reported</p> <p><i>Attrition</i> Overall, % 12%</p> <p>At end of treatment, % G1: 15.4 G2: 8.3</p> <p>At end of followup, % NR</p>

Evidence Table 6. KQ1 active versus control: Tier 3

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	waveform and bilateral anterior temporal placement of the electrodes.		<p><i>HAM-D 17</i> Baseline score, mean (SD)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 26.6 (SEM 2.8) G2: 24.1 (3.5)</p>		<p>Withdrawals due to efficacy, % G1: 7.7 G2: 8.3</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other</p> <p><i>Adherence/ compliance</i> None reported</p>

Evidence Table 7. KQ1 Non-pharm versus pharm

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Bretlau, 2008⁴¹</p> <p><i>Country, setting</i> Denmark, setting NR, outpatients</p> <p><i>Funding</i> Commercial source-please list name.supported by Medicon Valley Academy and an unrestricted research grant from H Lundbeck A/S</p> <p><i>Research Objective</i> To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment phase.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 49</p> <p><i>Duration</i> • 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. • Escitalopram was administered during entire trial at 20mg daily (10 mg daily for first wk of trial). • Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals.</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo</p>	<p><i>TRD definition required to be in current episode</i> Yes</p> <p><i>Tier 2</i></p> <p><i>Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i> • Aged 18 - 75 years; • meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); • failed to respond to at least one previous adequate (at least 6 weeks) antidepressant treatment during the current episode; • subjects with heart disorders or diabetes were included if they were in a somatically stable phase</p> <p><i>Exclusion criteria</i> • Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders;</p>	<p><i>Subgroups</i> No sub-group analysis</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 100 G2: 100</p> <p>Failed 2 or more, % NR</p> <p>Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9)</p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar NR</p> <p>Patient Characteristics Age, mean yrs G1: 53.1 G2: 57.8</p> <p>Sex, % females G1: 68% G2: 57%</p> <p>Race, % white NR</p> <p>Not Specified, % NR</p>	<p><i>HAM-D17</i> G1 G2:Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1),G1: = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2)</p> <p>Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2</p> <p>Responders, n G1: NR G2: NR</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall NR</p> <p>Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00</p> <p>Cardiovascular adverse events, % G1: palpitations: 3wk/ 12 wk mean: 0.23/0.14 G2: 0.30/0.12</p> <p>Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22</p> <p>Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06</p> <p>Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n = 24)</p> <p>G1: rTMS + escitalopram G2: sham TMS + escitalopram</p> <p>G1: rTMS + escitalopram** G2: sham TMS + escitalopram**</p> <p><i>Parameters</i> Location = Left Dorsolateral prefrontal cortex Frequency = 8 Hz Intensity = 90% motor threshold Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. Number of sessions = 15</p> <p><i>Strategy</i> Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment</p>	<ul style="list-style-type: none"> potential risk factors for escitalopram such as hypersensitivity to the Intervention, intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, pregnancy or insufficient contraception in females of reproductive age; risk factors for TMS such as history of epilepsy, metal implants in the head or neck regions, pacemaker or other electronic implants, receiving antipsychotics; having major suicide ideation. 	<p>Right handed, % NR</p> <p><i>Baseline n</i> G1:25 G2:24</p> <p>Groups similar at baseline Yes</p> <p><i>HAM-D17</i> Baseline score, mean* (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5)</p> <p>*based on rTMS: n = 22 sham: n = 23</p>	<p>Remitters, n G1: NR G2: NR</p> <p>Other • The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favor of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). • HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney <i>P</i> = 0.83 (0.22-1.44), <i>P</i> = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney <i>P</i>: 0.78 (0.18 - 1.39), <i>P</i> = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney <i>P</i>: 0.48(-0.12 - 1.07), <i>P</i> = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney <i>P</i>: 0.64 (0.04 - 1.24), <i>P</i> = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney <i>P</i>: 0.47 (</p>	<p>Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (<i>P</i> <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse events include: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 = 0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>-0.11 - 1.07), $P = 0.22$; • HAM-D6 Awk 2 Effect size (95% CI) and Mann-Whitney $P: 0.73$ (.018 -1.39), $P = 0.05$; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney $P: 0.80$ (0.20 - 1.42), $P = 0.01$; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney $P: 0.65$ (0.09 -1.29), $P = 0.02$; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney $P: 0.50$ (-0.10 -1.09), $P = 0.10$; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney $P: 0.50$ (-0.10 - 1.09), $P = 0.09$;</p> <p>BDI G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0)</p>	<p>12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined Yes</p> <p>MMSE No NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7), FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9) Change, mean (SD) G1: 12.4 G2: 9.4 Responders, n NR Remitters, n NR Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann-Whitney $P = 0.73$ (0.12 - 1.33), $P = 0.03$; Awk 3 Effect size (95% CI) and Mann-Whitney $P = 0.84$ (0.24 -1.46), $P = 0.00$; FU wk 5 Effect size (95% CI) and Mann-Whitney $P = 0.64$(0.02 - 1.22), $P = 0.03$; FU wk 8 Effect size (95% CI) and</p>	<p>Baseline n NR Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) NR Other <i>Other</i> Yes Study utilized the UKU scale as listed before - Other adverse events include: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Mann-Whitney P: 0.65 (0.04 - 1.24), P = 0.03; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.46 (-0.12 - 1.06), P = 0.12;</p> <p>MADRS NR</p> <p>IDS NR</p> <p>CGI-S NR</p> <p>CGI-I NR</p> <p>Instrument Major Depression Inventory (MDI) Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22 Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6) Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7)</p>	<p>=0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p>Adequate information Yes</p> <p><i>Attrition</i> Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8) Change, mean (SD) G1: 17.4 G2: 14.4 MDI Awk 2 Effect size (95% CI) and Mann-Whitney $P = 0.36$ (-0.23 - 0.94), $P = 0.18$; Awk 3 Effect size (95% CI) and Mann-Whitney $P: 0.43$ (-0.16 - 1.03), $P = 0.29$; FU wk 5 Effect size (95% CI) and Mann-Whitney $P: 0.29$ (-0.29 - 0.88), $P = 0.20$; FU wk 8 Effect size (95% CI) and Mann-Whitney $P: 0.22$ (-0.36 - 0.81), $P = 0.72$; FU wk 12 Effect size (95% CI) and Mann-Whitney $P: 0.23$ (-0.36 - 0.81), $P = 0.43$;</p>	<p>in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out. At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0 At end of follow-up, % G1: 21% G2: 4% Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR Adherence/ compliance NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Folkerts et al., 1997⁴²</p> <p><i>Country, setting</i> Germany, single center, inpatients</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To compare ECT in a controlled, randomized study with serotonin reuptake inhibitor paroxetine in treatment-resistant depression.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> per protocol</p> <p><i>N</i> 39</p> <p><i>Duration</i> Total 6 weeks; Wash-out >= 3days; Phase I ECT - 2wks, Paroxetine - 4 wks; Phase II Paroxetine group - if clinical improvement reduction < 50% treatment switched to ECT, ECT group crossed over to Paroxetine or other antidepressants.</p> <p><i>Interventions</i> G1: ECT G2: Paroxetine</p> <p><i>Medications Allowed</i> After med wash -out patients were allowed a tranquilizer (diazepam up to 5 mg daily), a sedative (lormetazepam 0.5- 1.0 mg or triazolam 0.25 mg) or a sedative neuroleptic (pipamperon, up to 40 mg daily).</p>	<p><i>TRD definition</i> • 2+ failed treatmentd (8+ weeks) including at least 1 tricyclic, at a dosage of at least 100 imiprimine equivalents • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major depressive episode single and recurrent • Bipolar disorders • HAM-D21 >=22</p> <p><i>Exclusion criteria</i> • Psychosis • Pronounced suicidal tendency • Severe physical illness • History of substance abuse • previous paroxetine or ECT treatment</p>	<p><i>Treatment Failure</i> Level of tx resistance (Kuhs, 1995) G1: 1.9 (0.7 SD) G2: 2.0 (0.8 SD) Mean failed trials G1: 4.9 G2: 4.3</p> <p><i>Polarity, %</i> Unipolar G1: 90.5 G2: 83.3</p> <p>Bipolar G1: 9.5 G2: 16.7</p> <p>Age, mean yrs G1: 47.6 G2: 52.3</p> <p>Sex, % females G1: 62 G2: 44</p> <p><i>HAM-D 21</i> Baseline n G1: 21 G2: 18 Baseline score, mean (SD) G1: 31.1 (4.9) G2: 32.6 (5.4)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) Endof Phase I (ECT: 2-3 wks, Paroxetine: 4 wks) G1: 12.5 (3.9) G2: 23.0 (10.4)</p> <p>Endof Phase II (open trial, 6 weeks) G1: 12.8 (5.1) G2: 15.2 (7.9)</p> <p>Change, mean (SD) End of Phase I G1: -18.6 G2: -9.6</p> <p>% Reduction in HAM-D, P = 0.001 End of Phase II G1: 18.3 G2: 17.4</p> <p>Responders, n End of Phase I G1: 15 (71.4%) G2: 5 (27.8%) P= 0.006</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 0 - all patients continued to scheduled end of treatment</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % 0</p> <p>Withdrawals due to efficacy, % 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> • All pts continued their respective therapies through scheduled end of treatment Phase I • 11 of 21 ECT were able to discontinue after 6th ECT session and 10 pts. had 3 additional ECT treatments. • Phase II - of ECT group, 9 received</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> ECT: • % receiving bilateral: 0 • Intensity: 2.5-fold seizure threshold • Number of sessions (range, mean, SD): 3/wk, range 6 to 9, mean 7.2 session</p> <p>Paroxetine • Started at 20 mg/day, within 7 days increased to 40 mg, allowed up to 50 mg, mean dose 44 mg/day for at least 4 weeks</p> <p><i>Strategy</i> Switch</p>				<p>paroxetine and 12 received other antidepressants • Of paroxetine groups, 7 crossed over to ECT • 11 received antidepressants - 7 paroxetine and 4 received other antidepressants • 1 person was excluded from analysis due to failure to increase treatment dosage</p>
<p><i>Author, Year</i> Moore et al., 1997⁴³</p> <p><i>Country, setting</i> Scotland, University clinic, outpatients</p> <p><i>Funding</i> Scottish Office, Home and Health Department</p> <p><i>Research Objective</i> To compare CBT to additional meds in treatment of depression non-responsive to medication during acute phase of study (results</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers confirmed with ITT</p> <p><i>N</i> 13</p> <p><i>Duration</i> 12 months</p> <p><i>Interventions</i> G1: Medication G2: Cognitive Therapy</p>	<p><i>TRD definition</i> • Failure to respond to AD medication during 16 wk acute txt phase • Failure required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • HAM-D > 14</p> <p><i>Exclusion criteria</i> NA</p>	<p>Baseline N G1: 6 G2: 7</p> <p><i>Treatment Failure</i> Current episode failures, mean G1: NR G2: NR</p> <p>Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100</p>	<p>Analyzed, n G1: 4 G2: 5</p> <p><i>HAM-D 17</i> Endpoint score, mean (SD) 4 mos G1: 11.0 (2.3) G2: 19.8 (5.6)</p> <p>8 mos G1: 6.6 (7.3) G2: 17.5 (1.9)</p> <p>12 mos G1: 5.0 (5.7) G2: 14.3 (4.0)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 31% At end of treatment, % G1: 43 G2: 17 At end of follow-up, % G1: 43 G2: 17</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>of Phase 1 reported elsewhere).</p> <p><i>Quality Rating</i> Fair</p>	<p>Medication Allowed G1: Continued AD assigned in acute phase OR initiated another AD txt G2: Discontinued AD</p> <p><i>Strategy</i> Mixed-between group differences</p> <p><i>Parameters</i></p> <ul style="list-style-type: none"> • Medication dose within recognized therapeutic threshold • Psychotherapy • Type of therapy: Cognitive Therapy • Method: NR • Number of sessions/week: min. 3/wk for 4wks and then 2/wk for 4wks and 1/wk for 4wks • Total number of sessions: NR 		<p><i>Age, mean yrs</i> Overall: 38</p> <p><i>Sex, % females</i> Overall: 62</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 18.6 (3.3) G2: 18.3 (3.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 30.6 (5.1) G2: 37.8 (5.1)</p>	<p>Completers, group by time, $P < 0.01$ ITT (LOCF), group by time, $P < 0.01$</p> <p>Change, mean (SD) 4 month G1: -7.6 G2: +1.5</p> <p>Partial responders, n Defined as HAM-D ≤ 14 G1: 5 G2: 2 $P = 0.17$</p> <p>Full responders, n Defined as HAM-D ≤ 6 G1: 3 G2: 0 $P = NR$</p> <p><i>BDI</i> Endpoint score, mean (SD) 4 mos. G1: 22.2 (5.9) G2: 41.5 (5.8) 8 mos. G1: 9.2 (8.3) G2: 34.3 (12.0) 12 mos. G1: 10.8 (12.2) G2: 35.8 (12.6) Group by time, $P = 0.05$ ITT (LOCF), group by time, $P < 0.05$</p>	<p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Change, mean (SD) At 4 months G1: -8.4 G2: +3.7</p> <p>Partial responders, n Defined as BDI ≤ 16 G1: 4 G2: 0 P < 0.05</p> <p>Full responders, n Defined as BDI ≤ 9 G1: 3 G2: 0 P = NR</p>	
<p><i>Author, Year</i> Thase et al, 2007⁴⁴</p> <p><i>Country, setting</i> United States, 18 primary care and 23 psychiatric care practice settings, outpatients</p> <p><i>Funding</i> National Institutes of Mental Health</p> <p><i>Research Objective</i> To compare the effectiveness of cognitive therapy and pharmacotherapy as second-step strategies for outpatients with major depressive disorder who had</p>	<p><i>Study design</i> Equipose-stratified randomization</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 304</p> <p><i>Duration</i> up to 14 weeks; Interventions G1: Augmentation Cognitive Therapy G2: Augmentation Medication G3: Switch Cognitive Therapy G4: Switch Medication</p>	<p><i>TRD definition</i> • Failed at least one adequate (8 wks or more) treatment in the current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> 18 to 75 years; non-psychotic major depressive disorder. HAM-D 17 > 14</p> <p><i>Exclusion criteria</i> • Remission in initial phase • Bipolar disorder • Schizophrenia, schizo affective disorder, or psychosis not otherwise specified</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 40.6 G2: 39.7 G3: 43.4 G4: 41.5</p> <p><i>Sex, % females</i> G1: 63.1 G2: 66.7 G3: 61.1 G4: 61.6</p> <p><i>Race, % white</i> G1: 80.0 G2: 84.6 G3: 77.8 G4: 73.3</p>	<p><i>HAM-D 21</i> Change, mean (SD) NR</p> <p><i>Remitters, n (%)</i> HAM-D < 8 G1: 15 (23.1%) G2: 39 (33.3%) G3: 9 (25.0%) G4: 24 (27.9%) P = 0.1967 P = 0.6881</p> <p><i>QIDS-SR</i> Mean Score at Endpoint G1: 8.2 (5.1) G2: 8.2 (4.8) G3: 9.1 (5.4) G4: 9.1 (5.0) P = 0.9490 P = 0.9734</p>	<p><i>Quality of Life</i> Baseline n G1: 65 G2: 117 G3: 36 G4: 86</p> <p><i>Baseline score, mean (SD)</i> G1: 41.8 (13.5) G2: 47.7 (14.9), P = 0.0202 G3: 43.3 (14.7) G4: 45.5 (13.4), P = 0.4634</p> <p><i>Endpoint score, mean (SD)</i> NR</p> <p><i>Change, mean (SD)</i> NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>received inadequate benefit from an initial trial of citalopram.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Medications allowed</i> See parameters</p> <p><i>Strategy</i> Mixed- between group differences</p> <p><i>Parameters</i> G1: Augmentation to citalopram with Cognitive Therapy: 16 sessions in 12 weeks G2: Augmentation to citalopram with sustained-release bupropion, buspirone G3: Switch from citalopram to cognitive therapy: 16 session in 12 weeks G4: Switch from citalopram to sertraline, sustained-release bupropion, or extended-release venlafaxine</p>	<ul style="list-style-type: none"> • Anorexia or bulimia • Obsessive compulsive disorder • Clear-cut intolerability to, or lack of effect with, an adequate trial of at least 1 protocol medication or other SSRI in current episode of MDD • Non response to 16 or more sessions of CT or > 7 ECT • General medical condition or medication that contraindicates any level 1 or 2 treatment option • Immediate hospitalization for substance/alcohol detoxification or treatment or psychiatric disorder(s). • Antipsychotic medication or mood stabilizers • Pregnant 	<p><i>HAM-D 21</i> Baseline n G1: 65 G2: 117 G3: 36 G4: 86 Baseline score, mean (SD) G1: 17.8 (5.7) G2: 16.0 (6.7) <i>P</i> = 0.0962 G3: 16.4 (6.2) G4: 17.7 (6.6) <i>P</i> = 0.3492</p> <p><i>QIDS-SR</i> Mean Score at Baseline G1: 11.9 (4.3) G2: 12.0 (4.6) <i>P</i> = 0.9495 G3: 11.2 (4.3) G4: 12.1 (4.6) <i>P</i> = 0.3282</p>	<p>Mean Score Change G1: -29.8 (40.5%) G2: -28.3 (39.6%) <i>P</i> = 0.8302 G3: -15.6 (40.7%) G4: -17.2 (46.2%) <i>P</i> = 0.9040</p> <p>Responders, n (%) G1: 23 (35.4%) G2: 33 (28.2%) <i>P</i> = 0.2493 G3: 8 (22.2%) G4: 23 (26.7%) <i>P</i> = 0.8390</p> <p>Remitters, n (%) QIDS-SR <6 G1: 20 (30.8%) G2: 39 (33.3%) <i>P</i> = 0.7803 G3: 11 (30.6%) G4: 23 (26.7%) <i>P</i> = 0.9032</p>	<p><i>Adverse Events</i> Maximum side effect frequency <i>P</i> = 0.1059 No side effects, n (%) G1: 20 (33.3) G2: 19 (17.3) G3: 2 (100) G4: 14 (18.4) 10–25% of the time, n (%) G1: 16 (26.7) G2: 38 (34.5) G3: 0 (0.0) G4: 25 (32.9) 50–75% of the time, n (%) G1: 13 (21.7) G2: 33 (30.0) G3: 0 (0.0) G4: 18 (23.7) 90–100% of the time, n (%) G1: 11 (18.3) G2: 20 (18.2) G3: 0 (0.0) G4: 19 (25.0) Maximum side effect intensity, <i>P</i> = 0.1164 No side effects, n (%) G1: 19 (31.7) G2: 19 (17.3) G3: 2 (100) G4: 13 (17.1) Minimal to mild, n (%) G1: 16 (26.7) G2: 33 (30.0) G3: 0 (0.0) G4: 26 (34.2)</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Moderate to marked, n (%) G1: 21 (35.0) G2: 42 (38.2) G3: 0 (0.0) G4: 27 (35.5)</p> <p>Severe to intolerable, n (%) G1: 4 (6.7) G2: 16 (14.5) G3: 0 (0.0) G4: 10 (13.2)</p> <p>Maximum side effect burden, <i>P</i> = 0.1314 No side effects, n (%) G1: 22 (36.7) G2: 24 (21.8) G3: 2 (100) G4: 18 (23.7)</p> <p>Minimal to mild, n (%) G1: 25 (41.7) G2: 47 (42.7) G3: 0 (0.0) G4: 32 (42.1)</p> <p>Moderate to marked, n (%) G1: 11 (18.3) G2: 32 (29.1) G3: 0 (0.0) G4: 22 (28.9)</p> <p>Severe to intolerable, n (%) G1: 2 (3.3) G2: 7 (6.4) G3: 0 (0.0) G4: 4 (5.3)</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Exited because of intolerance, n (%) G1: 6 (9.2) G2: 22 (18.8), $P = 0.0863$ G3: 6 (16.7), G4: 23 (26.7), $P = 0.2330$</p> <p>At least 1 serious adverse event, n (%) G1: 4 (6.2) G2: 4 (3.4), $P = 0.4588$ G3: 0 (0.0) G4: 2 (2.3), $P = 1.0000$</p> <p>At least 1 psychiatric serious adverse event, n (%) G1: 4 (6.2) G2: 1 (0.9), $P = 0.0556$ G3: 0 (0.0) G4: 0 (0.0)</p> <p><i>Attrition</i> Overall % NR</p> <p><i>Adherence/ compliance</i> Completed \geq CBT session G1: 17 (27.4%) G2: NR G3: 10 (34.5%) G4: NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Dannon, 2002⁴⁵</p> <p><i>Country, setting</i> Israel; medical center outpatient program</p> <p><i>Funding</i> National Association for Research in Schizophrenia and Affective Disorders (NARSAD) and Stanley Research Foundation</p> <p><i>Research Objective</i> To compare longitudinal outcomes of patients who responded to either rTMS or ECT</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Study references Grunhaus 2000 (Refid #368) which is open study of 40 patients - suspect this is continuation of this with additional patients. Of 43 responders initially identified, 2 are excluded</p> <p><i>N</i> 43</p> <p><i>Duration</i> 3 month and 6 month follow-up; Primary outcome was presence or absence of relapse at 3 or 6 months. Relapse defined as return of depressive symptomatology meeting DSM-IV criteria for MDD with a HAM-D17 score of >= 16 points</p> <p><i>Interventions</i> A - Electroconvulsive Therapy (ECT) B - Repetitive Transcranial Magnetic Stimulation (rTMS)</p>	<p><i>TRD definition</i> • Not required or not specified to be in current episode</p> <p><i>Setting(s)</i> Outpatient</p> <p><i>Inclusion criteria</i> • Responded to treatment with either ECT or rTMS • over age 18 years • DSM-IV diagnosis of MDD with or without psychotic features • no personal or first-degree family history of seizure • no major medical, neurologic, or neurosurgical disorder. • Response for inclusion defined as HAM-D17 <= 10 or demonstrating 60% drop in HAM-D and final global assessment scale (GAS) >=60</p> <p><i>Exclusion criteria</i> NR in this article - but Grunhaus 2000 (Refid #368) reports that patients with additional axis-I diagnoses were excluded from the study</p>	<p><i>Subgroups</i> No sub-group analysis of psychosis although permitted in study</p> <p><i>Treatment Failure</i> Patients referred for ECT because of nonresponse or psychotic MDD Failed 1 or more, % G1: NR G2: NR Failed 2 or more, % G1: NR G2: NR Current episode failures, mean G1: NR G2: NR Mean failed trials G1: NR G2: NR Previous treatment, not specified, % G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR Bipolar II G1: NR G2: NR</p>	<p><i>HAM-D 17</i> Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 7.90 (4.54) G2: 7.75 (3.74)</p> <p>Endpoint score, mean (SD) At 3 months G1: 7.71 (5.03) G2: 6.40 (4.91) At 6 months G1: 8.40 (5.60) G2: 7.90 (7.14)</p> <p>Change, mean (SD) At 3 months G1: -0.01 G2: 1.35 At 6 months G1: -0.5 G2: -0.15</p> <p>Responders, n NR</p> <p>Remitters, n NR Relapse (HAM-D ≥ 16) At 3 months G1: 2 G2: 1</p>	<p><i>Quality of Life</i> Global Assessment of Functioning (GAF), or GAS Baseline n G1: 20 G2: 21 Baseline score, mean (SD) G1: 71.81 (10.39) G2: 72.50 (9.39)</p> <p>Endpoint score, mean (SD) At 3 months G1: 75.52 (13.81) G2: 79.75 (12.92) At 6 months G1: 72.8 (11.94) G2: 77.75 (17.13)</p> <p>Change, mean (SD) At 3 months G1: -3.71 G2: -7.25 At 6 months G1: -0.99 G2: -5.25</p> <p>Other 3 mos <i>P</i> = NS, CI - 12.69, 4.23; 6 mos <i>P</i> = NS, CI -14.40, 4.50</p> <p><i>Adverse Events</i> NR</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>G1: ECT G2: rTMS Antidepressants prescribed at end of ECT and rTMS for all patients</p> <p><i>Parameters</i> rTMS: Location = Left Dorsolateral Prefrontal Cortex Frequency = 10Hz Intensity = 90% MT Per Session = 6 sec trains with 30 sec interval in between at 20 times. Number of sessions = daily for 20 days ECT Methods: Location: Initially unilateral; switched to bilateral txt after 6th txt if HRSD had not decreased by >= 30% Threshold = 2.5 times threshold energy to maintain a seizure length of >= 25 sec. Number of sessions = NR</p> <p><i>Strategy</i> There is no description of whether participants were taking medications prior to treatment with ECT or rTMS. Co-medications were not</p>		<p>Age, mean yrs G1: 57.43 G2: 56.85 Sex, % females G1: 70% Note: there might be a typo in table in reporting gender ratio, percentage reported here is based on numbers in "rTMS" column in paper because they add up to correct n for "ECT column." G2: 66.7% Race, % white G1: NR G2: NR Right handed, % G1: NR G2: NR</p> <p>Groups similar at baseline No- what are differences All <i>P</i> values were reported as non-significant for baseline characteristics, however following characteristics showed some variation between groups: Duration of episode (months) (mean +/- SD), ECT group = 6.71 +/- 7.56, rTMS group</p>	<p>At 6 months G1: 2 G2: 3 Combined G1: 4 G2: 4</p> <p>Other HAM-D17 3 mos = <i>P</i> = NS, CI -1.83, 4.46; 6 mos = <i>P</i> = NS, CI -3.61, 4.61 ECT vs. rTMS</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> No NR</p> <p>Baseline n NR</p> <p>Endpoint score, mean (SD) NR</p>	<p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined NA - No AE data reported</p> <p><i>MMSE</i> NR <i>Attrition</i> Overall, % 4.6%</p> <p>At end of treatment, % NR At end of follow-up, % G1: 0 G2: 9</p> <p>Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % G1: NR G2: NR</p> <p>Other 43 people agreed to be part of study, two were dropped before final analysis, no explanation is given, and they are</p>

Evidence Table 7. KQ1 Non-pharm versus pharm (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>allowed during period when ECT or rTMS was given with exception of lorazepam. Antidepressants</p>		<p><i>Tier</i> Tier 3 only mention of whether participants failed any previous treatments is in Grunhaus (#368).</p>	<p>Achieving 1 or 2 score, %(SD) NR Other NR <i>Other</i></p>	<p>not included in final analysis. The Michigan Adequacy of Treatments (MATS) was also included in this study. MATS for ECT was 3 mos FU 1.92 (1.04 SD), 6 mos FU 1.82 (0.98 SD); rTMS 3 mos FU 2.28 (1.07 SD), 6mos 2.44 (1.03 SD). CI for 3 mos FU ECT vs. rTMS is -1.14 - 0.43, $P = N$ <i>Adherence/ compliance</i> NR</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Berman, 2007⁴⁶ Berman</p> <p><i>Country, setting</i> United States Multicenter, outpatient setting</p> <p><i>Funding</i> Bristol-Myers Squibb Co Otsuka Pharmaceutical Co</p> <p><i>Research Objective</i> To compare the efficacy, safety, and tolerability of aripiprazole vs. placebo as adjunctive treatment to standard antidepressant therapy in the treatment of an MDE in pts who have shown an incomplete response to ADT</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-ITT)</p> <p><i>N</i> Prospective tx phase: 781 Double-blind tx phase: 366 (4 did not receive medication and were not included)</p> <p><i>Duration</i> Prospective tx phase: 8 wks Double-blind tx phase: 6 wks Primary outcome MADRS total score at endpoint 8 wks. Additional efficacy measures collected weekly.</p> <p><i>Interventions</i> Antidepressant + (Augmenter vs. Placebo) G1: Placebo augmentation G2: aripiprazole augmentation Attrition based on mITT NA</p>	<p><i>TRD definition</i> • Failed two or more adequate treatment failures (> 6 wk duration). • OR Inadequate response to at least 1 and no more than 3 adequate AD trials (> 6 wks duration at adequate dose) prior to inclusion. • Pts also had to establish inadequate antidepressant response in prospective treatment phase (8 wk duration) • Required a failure current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Outpatients 18-65 years; could understand, comply, and provide written consent. • MDE lasting ≥ 8 wks prior to inclusion without adequate response • At least 1, no more than 3 adequate AD trials without adequate response.</p>	<p><i>Subgroups</i> NA - KQ1 Drug Study</p> <p><i>Baseline n</i> G1: 178 G2: 184</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 100.0 G2: 100.0</p> <p>Failed 2 or more, % G1: 100 G2: 100</p> <p>Current episode failures, mean Failed 2+ in current episode G1: 33.6 G2: 33.5</p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 100</p> <p>Bipolar I G1: 0 G2: 0</p>	<p><i>HAM-D (Insert #)</i> NR</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> Yes G1: Placebo Augmenter G2: aripiprazole Augmenter</p> <p>Baseline n mITT Population G1: 172 G2: 181</p> <p>Baseline score, mean (SD) G1: 25.9 (6.5) G2: 26.0 (6.1)</p> <p>Endpoint score, mean (SD) Calculated endpoint score G1: 20.1 (NR) G2: 17.2 (NR)</p> <p>Change, mean (SD) Endpoint (6wk) G1: -5.8 G2: -8.8 G1: vs. G2, <i>P</i> < 0.001</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p> <p>Measures, Results NA</p> <p>Predefined NA</p> <p>MMSE NR</p> <p><i>Other</i> NA</p> <p><i>Attrition</i> Overall, % Double-blind tx phase: 10% (mITT); 11.6% (ITT)</p> <p>At end of treatment, % G1: 9.1% G2: 12.1%</p> <p>At end of followup, % NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Medications Allowed</i> Augmentation - Distribution of Ad at randomization: Escitalopram 29.6%; fluoxetine 14.2%, paroxetine 8.9%, sertraline 19.8%, venlafaxine 27.4%</p> <p><i>Strategy</i> Other, please explain: Prospective tx phase - switch strategy; Double-blind treatment phase - augmentation strategy</p> <p><i>Parameters</i> G1: Placebo G2: 5-20 mg/day</p>	<ul style="list-style-type: none"> HAM-D17 Total score ≥ 18; For continuation into double-blind tx phase HAM-D17 total score representing <50% reduction in symptoms during prospective tx phase, HAM-D17 total score ≥ 14; CGI-I score of ≥ 3 Most psychotropic meds, including benzodiazepines and other hypnotics discontinued. <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Current Axis I diagnosis of delirium, dementia, amnesic, or other cognitive disorder, panic disorder, or post traumatic stress disorder. Current Axis II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Pts experiencing hallucinations, delusions, or any psychotic symptomatology in the current episode 	<p>Bipolar II G1: 0 G2: 0</p> <p><i>Patient Characteristics</i></p> <p><i>Age, mean yrs</i> G1: 44.2 G2: 46.5</p> <p><i>Sex, % females</i> G1: 64.2 G2: 61.5</p> <p><i>Race, % white</i> G1: 92.6 G2: 87.4</p> <p><i>Not Specified, %</i> G1: 0 G2: 0</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) NR</p> <p><i>BDI</i> Baseline score, mean (SD)</p>	<p>Week 2 G1: -3.4 G2: -6.3 G1: vs. G2, $P < 0.001$</p> <p>Responders, n Endpoint (6wk) G1: 23.8% (n = 41) G2: 33.7% (n = 61) G1: vs. G2, $P = 0.027$</p> <p>Week 5 G1: 20.3% G2: 33.1% G1: vs. G2, $P < 0.01$</p> <p>Week 4 G1: 15.7% G2: 30.4% G1: vs. G2, $P < 0.001$</p> <p>Week 3 G1: 15.7% G2: 25.4% G1: vs. G2, $P < 0.05$</p> <p>Week 2 G1: 8.1% G2: 16.6% G1: vs. G2, $P < 0.05$</p>	<p>Withdrawals due to efficacy, % G1: 1.1% G2: 1.1%</p> <p>Withdrawals due to adverse events, % G1: 2.3% G2: 3.3%</p> <p>Other</p> <p><i>Adherence/ compliance</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<ul style="list-style-type: none"> • Significant substance use disorder within 12 months. • Allergy, hypersensitivity, or previous unresponsiveness to aripiprazole. • Participation in a clinical trial w/ aripiprazole or any other investigational product within past month • History of thyroid pathology, neuroleptic malignant syndrome, serotonin syndrome. • History of seizure disorder • Positive screen for drugs of abuse • Receipt of adjunctive antipsychotic + antidepressant for ≥ 3 wks during current episode • Receipt of ECT for current episode • Inadequate response to previous ECT in any episode 	NR	<p>Week 1 G1: 1.8% G2: 6.2% G1: vs. G2, <i>P</i> = 0.025</p> <p>Remitters, n Endpoint G1: 15.7% (n = 27) G2: 26.0% (n = 47) G1: vs. G2, <i>P</i> = 0.011</p> <p>Week 5 G1: 14.0% G2: 26.0% G1: vs. G2, <i>P</i> < 0.01</p> <p>Week 4 G1: 11.0% G2: 22.7% G1: vs. G2, <i>P</i> < 0.01</p> <p>Week 3 G1: 8.7% G2: 18.8% G1: vs. G2, <i>P</i> = 0.006</p> <p>Week 2 G1: 5.8 G2: 10.5 G1: vs. G2, <i>P</i> = NS</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Week 1 G1: 1.8 G2: 3.4 G1: vs. G2, P = NS</p> <p>Other Response defined as \geq 50% reduction in MADRS total score. Remission defined as response plus an absolute MADRS total score of \leq 10. <i>IDS</i> G1: Placebo G2: aripiprazole[Q60]</p> <p>Baseline n ITT Population G1: 172 G2: 181</p> <p>Baseline score, mean (SE) G1: 34.0 (1.1) G2: 34.4 (1.0)</p> <p>Endpoint score, mean (SE) Calculated G1: 28.8 (NR) G2: 27.4 (NR)</p> <p>Change, mean (SE) G1: -5.2 (0.8) G2: -7.0 (0.8)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>$P = 0.076$ **Text reports "While differences on the IDS-SR were significant at weeks 2, 3, 4, and 5, significance was not shown at endpoint" Data not shown.</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>CGI-S Baseline n mITT Population G1: 172 G2: 181</p> <p>Baseline score, mean (SE) G1: 4.11 (0.05) G2: 4.08 (0.04)</p> <p>Endpoint score, mean (SE) Calculated G1: 3.47 (NR) G2: 3.05 (NR)</p> <p>Change, mean (SE) Endpoint G1: -0.64 (0.08) G2: -1.03 (0.08) G1: vs. G2, $P < 0.001$</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>CGI-I Baseline n G1: 172 G2: 181</p> <p>Endpoint score, mean (SE) G1: 2.81 (0.09) G2: 2.49 (0.08) G1: vs. G2, <i>P</i> = 0.003</p> <p>Achieving 1 or 2 score, %(SD) Endpoint: G1: 37.2 G2: 53.0 G1: vs. G2, <i>P</i> = 0.002</p> <p>Week 5: G1: 32.6 G2: 51.4 G1: vs. G2, <i>P</i> < 0.001</p> <p>Week 4: G1: 31.4 G2: 52.5 G1: vs. G2, <i>P</i> < 0.001</p> <p>Week 3: G1: 28.5 G2: 45.3 G1: vs. G2, <i>P</i> < 0.001</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Week 2: G1: 22.7 G2: 35.0 G1: vs. G2, P = 0.010 Week 1: G1: 12.2 G2: 18.3 G1: vs. G2, P = 0.123 Other NR	
<p><i>Author, Year</i> Berman, 2009⁴⁷</p> <p><i>Country, setting</i> United States Multicenter</p> <p><i>Funding</i> Bristol-Myers Squibb Co Otsuka Pharmaceutical Co</p> <p><i>Research Objective</i> To evaluate the efficacy and safety of adjunctive aripiprazole vs. antidepressant monotherapy in pts with MDD and independently replicate the positive findings of two similar trials.</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> mITT</p> <p><i>N</i> Prospective tx phase: 827 Double-blind tx phase: 349</p> <p><i>Duration</i> Prospective tx phase: 8 wks Double-blind tx phase: 6 wks Primary outcome MADRS total score at endpoint 8 wks.</p> <p><i>Interventions</i> Antidepressant + Augmenter vs. Placebo</p>	<p><i>TRD definition</i> Required to be in current episode Yes</p> <p><i>Tier 1</i></p> <p><i>Setting(s)</i> Not Clearly reported</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Patients 18-65 yrs of age • DSM-IV criteria for MDE lasting ≥ 8 wks. • Inadequate response to prior antidepressant to 1-3 antidepressant trials of ≥ 6wk duration. • Inclusion into double-blind tx phase required meeting criteria for inadequate response score from baseline to 	<p><i>Subgroups</i> NA - KQ1 Drug Study</p> <p><i>Baseline n</i> G1: 172 G2: 177</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 68.0 G2: 71.8</p> <p>Failed 2 or more, % G1: 100.0 G2: 100.0</p> <p>Current episode failures, mean Failed 2+ in current episode (%) G1: 29.1 G2: 26.6</p>	<p><i>N analyzed</i> G1: 169 G2: 174</p> <p><i>HAM-D (Insert #)</i> Yes HAM-D17 G1: Placebo augmentation G2: aripiprazole augmentation</p> <p>Endpoint score, mean (SD) Calculated: G1: 14.9 (NR) G2: 12.2 (NR)</p> <p>Change, mean (SD) G1: -5.1 (0.6 SE) G2: -7.6 (0.6 SE) G1: vs. G2, P <0.001</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p> <p><i>Measures, Results</i> NA</p> <p><i>Predefined</i> NA</p> <p><i>MMSE</i> NR</p> <p><i>Other</i> NA</p> <p><i>Adequate information</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Quality Rating</i> Fair</p>	<p>Augmenter G1: Placebo augmentation G2: aripiprazole augmentation G1: Placebo augmentation G2: aripiprazole augmentation NA</p> <p><i>Medications Allowed</i> All pts taking an antidepressant at randomization - Distribution - Aripiprazole Group: Escitalopram: 33.9%; fluoxetine: 17.5%; paroxetine: 7.9%; Sertraline 11.9%; Venlafaxine ER: 28.8% Placebo Group: excitalopram: 30.2%; fluoxetine: 14.5%; paroxetine: 11.6%; sertraline: 17.4%; venlafaxine ER: 26.2%</p> <p><i>Strategy</i> Augment</p> <p><i>Parameters</i> G1: Plabebo augmentation G2: 2-20 mg/day</p>	<p>end of prospective treatment phase, a HAM-D 17 total score of ≥ 14, and a CGI_I score ≥ 3 at wks 6 and 8.</p> <ul style="list-style-type: none"> Stable doses of hypnotics for insomnia, including benzodiazepines and other sleep aider discontinued ≥ 1 wk prior to prospective tx phase. All psychotropics prohibited. Txt of extrapyramidal symptoms permitted during study. <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Current Axis I diagnosis of delirium, dementia, amnestic, or other cognitive disorder, panic disorder, or post traumatic stress disorder. Current Axix II diagnosis of borderline, antisocial, paranoid, schizoid, schizotypal, or histrionic personality disorder. Pts experiencing hallucinations, delusions, or any 	<p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 100</p> <p>Bipolar I G1: 0 G2: 0</p> <p>Bipolar II G1: 0 G2: 0</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 45.6 G2: 45.1</p> <p><i>Sex, % females</i> G1: 68.0 G2: 78.0</p> <p><i>Race, % white</i> G1: 86.6 G2: 87.6</p> <p><i>Not Specified, %</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> No -</p>	<p>Responders, n NR</p> <p>Remitters, n NR</p> <p>BDI NR</p> <p>MADRS Yes G1: Placebo Augmenter G2: aripiprazole Augmenter</p> <p>Baseline n mITT (n analyzed) G1: 169 G2: 174</p> <p>Baseline score, mean (SD) G1: 27.1 (5.8) G2: 26.6 (5.8)</p> <p>Endpoint score, mean (SD) Calculated: G1: 20.7 (NR) G2: 16.5 (NR)</p> <p>Change, mean (SD) G1: -6.4 (NR) G2: -10.1 (NR) G1: vs. G2, $P < 0.001$ Treatment difference: - 3.7 (95%CI -5.4, -2.0)</p>	<p><i>Attrition</i> Overall, % Double-blind tx phase: 15.2%</p> <p>At end of treatment, % G1: 13.4 G2: 16.9</p> <p>At end of followup, % NA</p> <p>Withdrawals due to efficacy, % G1: 1.7 G2: 1.1</p> <p>Withdrawals due to adverse events, % G1: 1.7 G2: 6.2</p> <p>Other</p> <p><i>Adherence/ compliance</i></p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<p>psychotic symptomatology in the current episode</p> <ul style="list-style-type: none"> • Significant substance use disorder within 12 months. • Allergy, hypersensitivity, or previous unresponsiveness to aripiprazole. • Participation in a clinical trial w/ aripiprazole or any other investigational product within past month • History of thyroid pathology, neuroleptic malignant syndrome, serotonin syndrome. • History of seizure disorder. • Positive screen for drugs of abuse. • Receipt of adjunctive antipsychotic + antidepressant for ≥ 3 wks during current episode. • Receipt of ECT for current episode • Inadequate response to previous ECT in any episode 	<p>Aripiprazole group 138 females (78%) vs. Placebo 117 females (68%)</p> <p><i>HAM-D 17</i> Baseline score, mean (SE) G1: 20.0 (0.4) G2: 19.8 (0.4)</p> <p><i>BDI</i> Baseline score, mean (SD) NR</p>	<p>Responders, n G1: 26.6% (n = 45) G2: 46.6% (n = 81) G1: vs. G2, <i>P</i> < 0.001</p> <p>Remitters, n G1: 18.9% (n = 32) G2: 36.8% (n = 64) G1: vs. G2, <i>P</i> < 0.001</p> <p>Alternate definitions MADRS total score ≤ 12 G1: 27.2% G2: 43.7% G1: vs. G2, <i>P</i> < 0.001</p> <p>MADRS total score ≤ 8 G1: 14.2% G2: 27.6% G1: vs. G2, <i>P</i> < 0.01</p> <p>Other Response defined as ≥ 50% reduction in MADRS total score.</p> <p>Remission defined as ≤ 10 and ≥ 50% reduction in MADRS total score. Alternate Remission Definitions: MADRS total score ≤ 12; MADRS ≤ 8</p> <p>IDS Yes</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G1: Placebo Augmenter G2: aripiprazole Augmenter[Q60]</p> <p>Baseline n G1: 169 G2: 174</p> <p>Baseline score, mean (SE) G1: 33.0 (1.1) G2: 32.7 (1.1)</p> <p>Endpoint score, mean (SE) Calculated: G1: 27.6 (NR) G2: 25.8 (NR)</p> <p>Change, mean (SE) G1: -5.4 (1.1) G2: -6.9 (0.9) G1: vs. G2, <i>P</i> = 0.12</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>CGI-S Yes G1: Placebo Augmenter G2: aripiprazole Augmenter</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Baseline n G1: 169 G2: 174</p> <p>Baseline score, mean (SE) G1: 4.2 (0.1) G2: 4.1 (0.1)</p> <p>Endpoint score, mean (SE) Calculated: G1: 3.5 (NR) G2: 3.0 (NR)</p> <p>Change, mean (SE) G1: -0.7 (0.1) G2: -1.1 (0.1) G1: vs. G2, <i>P</i> <0.001</p> <p>CGI-I Yes G1: Placebo Augmenter G2: aripiprazole Augmenter</p> <p>Baseline n G1: 169 G2: 174</p> <p>Endpoint score, mean (SE) G1: 2.8 (0.1) G2: 2.4 (0.1) G1: vs. G2, <i>P</i> = 0.001</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Achieving 1 or 2 score, %(SD) G1: NR G2: NR</p> <p><i>Other</i> Validated measure Yes</p> <p>Instrument QIDS-SR</p> <p>Intervention G1: Placebo Augmenter G2: aripiprazole Augmenter</p> <p>Baseline n G1: 169 G2: 174</p> <p>Baseline score, mean (SE) G1: 12.8 (0.4) G2: 13.0 (0.4)</p> <p>Endpoint score, mean (SE) Calculated: G1: 10.7 (NR) G2: 10.2 (NR)</p> <p>Change, mean (SE) G1: -2.1 (0.3) G2: -2.8 (0.3) G1: vs. G2, P = 0.08</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Corya et al., 2006⁴⁸</p> <p><i>Country, setting</i> Multinational, 16 countries, 90 centers</p> <p><i>Funding</i> Eli Lilly</p> <p><i>Research Objective:</i> Olanzapine/fluoxetine combination (OFC) was examined in comparison with olanzapine, fluoxetine, and venlafaxine in a TRD population.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N:</i> 483</p> <p><i>Duration:</i> 12 weeks</p> <p><i>Primary outcome:</i> Change in MADRS at 12 weeks</p> <p><i>Interventions</i> G1: Olanzapine/fluoxetine G2: Olanzapine G3: Fluoxetine G4: Venlafaxine G5: Low-dose Olanzapine/fluoxetine</p> <p><i>Parameters</i> G1: Olanzapine/fluoxetine: Combined 4 groups G2: Olanzapine: 6 or 12 mg/d G3: Fluoxetine: 25 or 50 mg/d G4: Venlafaxine: 75-375 mg/d G5: Low-dose Olanzapine/fluoxetine: 1mg/d olanzapine, 5 mg fluoxetine</p>	<p><i>TRD definition:</i> “...documented history of a failure to achieve a satisfactory response to a selective serotonin reuptake inhibitor (SSRI) antidepressant after at least 6 weeks of therapy at a therapeutic dose” and subsequently showing less than 30% improvement after 7 weeks of venlafaxine treatment; Failure within current episode</p> <p>Remission defined as MADRS ≤ 8 at two consecutive visits</p> <p><i>Setting(s)</i> <i>Inclusion criteria:</i> 18 years ; CGI-S 4 or greater, MDD w/o psychotic features; documented history of TRD</p> <p><i>Exclusion criteria:</i> schizophrenia, schizoaffective disorder; other psychotic disorders, bipolar I or II disorder, PTSD, MDD w/ seasonal pattern, or dissociative disorders; pregnant or nursing; concomitant</p>	<p><i>Subgroups; none</i></p> <p><i>Treatment Failure</i> Failed 2 or more, 100%</p> <p>Current episode failures, mean NR</p> <p>Mean failed trials</p> <p><i>Polarity, %</i> Unipolar 100%</p> <p><i>Age, mean yrs</i> Overall: 45.7</p> <p><i>Sex, % females</i> Overall: 72.5%</p> <p><i>Race, % white</i> Overall: 89.9</p> <p><i>Right handed, %</i> NR and NA</p> <p>Groups similar at baseline</p> <p>Group baseline characteristics NR just overall</p> <p><i>Tier 1</i></p>	<p><i>HAM-D NR</i></p> <p><i>MADRS</i> Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59</p> <p>Baseline score, mean (SD) 30.0 (6.8) for overall sample (moderate-to-severe range)</p> <p>Endpoint score, mean (SD) NR Change, mean (SD) G1: -14.06 (0.59) G2: -7.71 (1.17) G3: -11.70 (1.14) G4: -13.73 (1.16) G5: -11.97 (1.13) G1: (OFC) vs. G2 (Ola), <i>P</i> < 0.001. all others NS Responders, n (%) G1: 100 (43.3) G2: 15 (25.4) G3: 19 (33.9) G4: 29 (50.0) G5: 20 (36.4) G! (OFC) vs. G2 (Ola), <i>P</i> = 0.017. all others NS</p>	<p><i>Quality of Life: NA</i></p> <p><i>Adverse Events: NA</i></p> <p><i>Neuropsychological or executive functioning: NA</i></p> <p><i>MMSE: NA</i></p> <p><i>Attrition: NA</i></p> <p><i>Adherence/ compliance: NA</i></p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i></p> <p>Switch</p>	<p>medications with primary CNS activity w/ exception of benzodiazepines up to an equivalent of 4mg of lorazepam per day</p>		<p>Remitters (MADRS \leq 8 for any two consecutive visits), n (%) G1: 69 (29.9) G2: 8 (13.8) G3: 10 (17.9) G4: 13 (22.4) G5: 11 (20.0) G1: (OFC) vs. G2 (Ola), <i>P</i> = 0.013. all others NS</p> <p>CGI-S Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR Change, mean (SD) G1: -1.51 (0.07) G2: - 0.91 (0.15) G3: -1.26 (0.15) G4: -1.49 (0.14) G5: -1.23 (0.14) G1: (OFC) vs. G2 (Ola), <i>P</i> < 0.001. all others NS</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				BPRS Baseline n G1: 243 G2: 62 G3: 60 G4: 59 G5: 59 Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: -6.01 (0.40) G2: --3.16 (1.04) G3: -4.82 (0.88) G4: -4.76 (0.98) G5: -6.33 (0.87) G1: (OFC) vs. G2 (Ola), P = 0.008. all others NS	
<p><i>Author, Year</i> Fang et al., 2010⁴⁹</p> <p><i>Country, setting</i> China - multicenter (8), both inpatient and outpatients included</p> <p><i>Funding</i> B10th Five-year Plan[of National Key Technologies R&D Program grants 2004BA720A21-02 (Ministry of Science and</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 150</p> <p><i>Duration</i> 8 weeks</p> <p><i>Interventions</i> G1: Venlafaxine-XR 225 mg/d (n = 50)</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Failed two or more adequate (12 weeks or more each) treatments from different classes in the current depressive episode. Required to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Ages of 18 and 65 years with a diagnosis 	<p><i>Subgroups</i> No</p> <p><i>Baseline n</i> G1: 50 G2: 55 G3: 45</p> <p><i>Treatment Failure</i> Failed 1 or more, % 100</p> <p>Failed 2 or more, % 100</p>	<p><i>HAM-D (17)</i> Endpoint score, mean (SD) G1: G2: G3: Change, mean (SD) NR</p> <p>Responders, n G1: 32 G2: 32 G3: 30</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p> <p><i>MMSE</i> NR</p> <p><i>Other</i> NR</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Technology of China) and the Climbing Mountain Action Plan[Program grants 064119533 (Science and Technology Commission of Shanghai Municipality) and partly supported by National High-tech R&D Program (863 Program) grants 2006AA02Z430 (Ministry of Science and Technology of China).</p> <p><i>Research Objective</i> Compare the efficacy and tolerability of antidepressants switch with extended-release venlafaxine (venlafaxine-XR), mirtazapine, and paroxetine in Chinese patients with MDD who had 2 consecutive unsuccessful antidepressant trials</p> <p><i>Quality Rating</i> Fair</p>	<p>G2: Mirtazapine45 mg/d (n = 55) G3: Paroxetine20 mg/d (n = 45) <i>Medications Allowed</i> All patients switched to a new pharmacotherapy</p> <p><i>Strategy</i> Switch strategy</p> <p><i>Parameters</i> venlafaxine-XR 225 mg/d (Effexor; Wyeth, China); mirtazapine, 45 mg/d (Remeron; Organon, China); and paroxetine, 20 mg/d (Paxil; GlaxoSmithKline)</p>	<p>of MDD based on the criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and from inpatient and outpatient services</p> <ul style="list-style-type: none"> • Meet stage 2 TRD criteria described by Thase and Rush. 9 Stage 2 TRD in this study was retrospectively and/or prospectively. <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Lifetime diagnosis of bipolar disorder, schizoaffective disorder, schizophrenia, or other psychotic disorders • Imminent risk for suicide or homicide judged by a research psychiatrist • Any medical contraindication to antidepressants or other psychotropic medication • Unstable general medical condition or a condition that required combination treatment of an antidepressant and any other psychotropic medication 	<p>Current episode failures, mean NR</p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100</p> <p>Bipolar I 0</p> <p>Bipolar II 0</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> Overall 40.5 years</p> <p><i>Sex, % females</i> Overall 54%</p> <p><i>Race, % white</i> NR</p> <p><i>Not Specified, %</i> 0</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes</p>	<p>Remitters, n G1: 21 G2: 20 G3: 21 Other There were no significant differences in the remission rates among the 3 groups (W2 = 1.097, df = 2, P = 0.578), Response Rates P = 0.664. There were also no significant differences among the groups in the cumulative proportion of remission rates at each postbaseline visit (log rank, W2 = 0.4974, df = 2, P = 0.7798).</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> Yes</p>	<p><i>Attrition</i> Overall, % 0.18 At end of treatment, % G1: 18.0% G2: 18.2% G3: 17.8%</p> <p>At end of followup, % NA</p> <p>Withdrawals due to efficacy, % G1: 2 G2: 6 G3: 6</p> <p>Withdrawals due to adverse events, % G1: 0 G2: 0 G3: 2</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		(including typical/atypical antipsychotic agents, mood stabilizers, anticonvulsants, and stimulants) • Modified electroconvulsive therapy within 1 month of study screening • Pregnant, planning to become pregnant, or breast-feeding	<i>HAM-D 17</i> Baseline score, mean (SD) Overall 24.6 (5.8) <i>BDI</i> Baseline score, mean (SD)	G1: Venlafaxine G2: Mirtazapine G3: Paroxetine Achieving 1 or 2 score, % (SD) CGI = 1 G1: 48.0 G2: 29.1 G3: 40.0 Other <i>P</i> = 0.136 Other NR	
<p><i>Author, Year:</i> Fava et al., 2006⁵⁰</p> <p><i>Country, setting:</i> USA, Multicenter 18 primary and 23 psychiatric centers</p> <p><i>Funding:</i> NIMH</p> <p><i>Research Objective:</i> Compared the efficacy of switching to mirtazapine vs. nortriptyline following two prospective, consecutive, unsuccessful medication treatments for non-psychotic MDD</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT N: 235</p> <p><i>Duration:</i> 12-14 weeks Interventions G1: Mirtazapine G2: Nortriptyline</p> <p><i>Parameters</i> G1: Mirtazapine: Up to 60mg/day G2: Nortriptyline: Up to 200mg/day</p> <p><i>Strategy:</i> Switch</p>	<p><i>TRD definition:</i> 2 or more in current episode. Remission defined as HAM-D17 ≤ 7</p> <p><i>Tier 1</i></p> <p><i>Setting(s)</i> Outpatient; Psychiatric and Primary Care Practices</p> <p><i>Inclusion criteria:</i> • Outpatients with a primary diagnosis of non-psychotic MDD</p> <p><i>Exclusion criteria:</i> • Psychotic disorders, OCD</p>	<p><i>Subgroups-</i> None</p> <p><i>Treatment Failure</i> Failed 1 or more, 100% Failed 2 or more, 100%</p> <p>Current episode failures, mean</p> <p>Overall: 2</p> <p>Failed trials, mean</p> <p>Overall: 2</p> <p>Previous treatment, not specified, 0%</p> <p><i>Polarity, %</i> Unipolar</p>	<p><i>HAM-D 17</i></p> <p>G1 G2: G1</p> <p>G2:Endpoint score, mean (SD) G1: NR G2: NR</p> <p>Change, mean (SD) G1: NR G2: NR Average percentage improvement G1: NR G2: NR Responders, n G1: NR G2: NR</p>	<p><i>Quality of Life:</i> NA</p> <p><i>Adverse Events:</i> NA</p> <p><i>Neuropsychological or executive functioning:</i> NA</p> <p><i>MMSE:</i> NA</p> <p><i>Attrition:</i> NA</p> <p><i>Adherence/ compliance:</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Quality Rating: Good</p>	<p>Diagnosis: 100% MDD</p>	<ul style="list-style-type: none"> • Eating disorders • General medical conditions contraindicating the use of protocol medications • Substance dependence (only if it required inpatient detoxification) • Pregnant • Breastfeeding. <p>Stable psychotropic medications allowed. Stimulant, anticonvulsant, antipsychotic mood stabilizing, nonprotocol antidepressants and potential antidepressant augmenting agents (e.g. busiprone) were not allowed. Anxiolytics (except alprazolam) and sedative hypnotics (including trazodone for sleep)</p>	<p>G1: 100 G2: 100 Bipolar I G1: 0 G2: 0 Bipolar II G1: 0 G2: 0 <i>Age, mean yrs</i> G1: 44.8 G2: 45.1 <i>Sex, % females</i> G1: 42.1 G2: 51.2 <i>Race, % white</i> G1: 80.7 G2: 76.0 <i>Right handed, %</i> NR <i>HAM-D 17</i> Baseline n G1: 114 G2: 121 Baseline score, mean (SD) G1: 19.8 (7.0) G2: 18.6 (5.9)</p> <p>Groups similar at baseline: Yes. More in mirtazapine 24.6% had attempted suicide vs. nortriptyline 12.4%, but this difference was controlled for in the analyses.</p>	<p>Remitters, n G1: 14 (12.3%) G2: 24 (19.8%) G1: vs. G2, P=0.27</p> <p><i>QIDS-SR</i> Baseline n G1: 114 G2: 121 Baseline score, mean (SD) G1: 14.1 (5.0) G2: 14.0 (4.7) Endpoint score, mean (SD) G1: 12.6 (5.4) G2: 12.2 (5.9)</p> <p>Change, mean (SD): NR Average percentage improvement G1: -7.1% (35.2) G2: -10.9 (36.5) G1: vs. G2, p=0.48</p> <p>Responders (50% reduction), n G1: 15 (13.4%) G2: 20 (16.5%) G1: vs. G2, p=0.57</p> <p>Remitters (< 5), n G1: 9 (8.0%) G2: 15 (12.4%)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Mazeh et al., 2007⁵¹</p> <p><i>Country, setting</i> Israel, inpatient, single center</p> <p><i>Funding:</i> NR</p> <p><i>Research Objective:</i> compare the efficacy and tolerability of venlafaxine vs. paroxetine in elderly patients suffering from resistant major depression</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N= 30</i></p> <p><i>Duration:</i> 6 weeks</p> <p><i>Interventions</i> G1: Paroxetine (mean 26 mg/day) G2: Venlafaxine (165 mg/day)</p> <p><i>Parameters</i> G1: Paroxetine: 10-60mg/d(mean 26 mg/day) G2: Venlafaxine 75-300mg/d (mean 165 mg/day)</p> <p><i>Strategy –</i> Switch</p>	<p><i>TRD definition:</i> “...they did not respond to two adequate pharmacological treatments for depression during this depressive episode.”</p> <p>Remission defined as HAM-D21 ≤ 7</p> <p><i>Setting(s); Mental Health Center</i></p> <p><i>Inclusion criteria; MDD; 18 or more on Ham-D21 ;inpatient; ≥ 65 years old</i></p> <p><i>Exclusion criteria; Dementia; exposure to study drugs</i></p> <p><i>Diagnosis</i> 100% MDD</p>	<p><i>Subgroups</i></p> <p><i>Treatment Failure</i> NR</p> <p><i>Polarity, %</i> Unipolar NR</p> <p><i>Age, mean yrs</i> G1: 77.7 G2: 74.1</p> <p><i>Sex, % females</i> G1: 60 G2: 53</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes <i>Tier</i> Tier 1</p>	<p><i>HAM-D 21</i> Baseline n G1: 15 G2: 15</p> <p>Baseline score, mean (SD) G1: 30.1 (7.9) G2: 26.3 (5.9)</p> <p>Endpoint score, mean (SD) G1: NR G2: NR Change, mean (SD) G1: -12.5 G2: -19.1 <i>P</i><0.0003</p> <p>Average percentage improvement G1: NR G2: NR</p> <p>Responders, n (%) G1: 8 (53) G2: 12 (80) <i>P</i> = NR</p> <p>Remitters, n (%) G1: 5 (33) G2: 9 (60) <i>P</i> = NR</p> <p>Data primarily reported in figures</p> <p>Other</p>	<p><i>Quality of Life:</i> NA</p> <p><i>Adverse Events:</i> NA</p> <p><i>Neuropsychological or executive functioning:</i> NA</p> <p><i>MMSE:</i> NA</p> <p><i>Attrition:</i> NA</p> <p><i>Adherence/ compliance:</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				CGI-S Baseline n G1: 15 G2: 15 Baseline score, mean (SD) G1: 5.7 (0.9) G2: 5.5 (0.7) Change, mean G1: - 2.3 vs. G2: - 2.3 P < 0.00002 GDS Baseline n G1: 15 G2: 15 Baseline score, mean (SD) G1: 11.7 (3.0) G2:12.3 (1.5) Change, mean (SD) G1: -3.2 G2: -6.0 P<0.2	
<p><i>Author, Year</i> McGrath et al., 2006⁵²</p> <p><i>Country, setting</i> United States Primary care and psychiatric care practice settings</p> <p><i>Funding</i> NIMH</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT N = 109</p> <p><i>Duration</i></p>	<p><i>TRD definition;</i> “...didnot achieve remission with, or were intolerant of, each of the first three levels of pharmacotherapy treatment.” 3 failed treatments in current episode. Remission defined as HAM-D21 ≤ 7</p>	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i> Failed 1 or more, 100% Failed 2 or more, 100%</p> <p>Current episode failures, mean 3</p> <p>Mean failed trials 3</p>	<p><i>HAM-D 17</i> Baseline n G1: 58 G2: 51 Baseline score, mean (SD) G1: 19.6 (7.6) G2: 19.7 (5.5)</p> <p>Endpoint score, mean (SD) NR:</p>	<p><i>Quality of Life:</i> NA</p> <p><i>Adverse Events:</i> NA</p> <p><i>Neuropsychological or executive functioning:</i> NA</p> <p><i>MMSE:</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i></p> <p>To compare the effectiveness and tolerability of tranylcypromine versus combination treatment with venlafaxine ER and mirtazapine in patients with treatment-resistant major depression.</p> <p><i>Quality Rating:</i></p> <p>Fair</p>	<p>12 -14weeks</p> <p><i>Interventions</i></p> <p>G1: Tranylcypromine G2: Venlafaxine ER + Mirtazapine</p> <p><i>Parameters</i></p> <p>G1: Tranylcypromine 10mg/d for 2wk, weekly increases of 10 mg/d until intolerance or 60 mg/d maximum G2: Venlafaxine ER + Mirtazapine: Venlafaxine 37.5 mg/d wk 1, 75 mg/d wk 2, 150 mg/d wks 3-5, 225 mg/d wks 6-8, 300 mg/d thereafter. Mirtazapine 15 mg/d wks 1-2, 30 mg/d next 8 wks, 45 mg/d thereafter</p> <p><i>Strategy - switch</i></p>	<p><i>Setting(s)</i></p> <p><i>Genera and psychiatric settings</i></p> <p><i>Inclusion criteria</i></p> <p>Primary diagnosis of nonpsychotic major depressive disorder by DSM-IV criteria; Did not achieve remission with or were intolerant of each of the first 3 levels of pharmacotherapy treatment in STAR*D</p> <p><i>Exclusion criteria</i></p> <p>NR</p> <p><i>Stable psychotropic medications allowed</i></p> <p>Not clearly reported</p>	<p>Previous treatment, not specified, 0%</p> <p><i>Polarity, %</i></p> <p>Unipolar Overall; 100%</p> <p>Bipolar I – 0%</p> <p>Bipolar II – 0%</p> <p><i>Age, mean yrs</i></p> <p>G1: 46.6 G2: 45.3</p> <p><i>Sex, % females</i></p> <p>G1: 56.9 G2: 45.1</p> <p><i>Race, % white</i></p> <p>G1: 79.3 G2: 84.3</p> <p><i>Right handed, %</i></p> <p>Overall NR</p> <p>Groups similar at baseline – Overall yes. Groups received different medications at STAR*D level 3 treatment; difference in exiting Level 3 treatment due to intolerance of treatment, but these were controlled for in analysis.</p> <p><i>Tier 1</i></p>	<p>Responders, n NR Remitters, 7 or less, n (%)</p> <p>G1: 4 (6.9) G2: 7 (13.7) P= NS</p> <p><i>QIDS SR</i></p> <p>Baseline score, mean (SD)</p> <p>G1: 13.6 (5.1) G2: 14.9 (4.1)</p> <p>Endpoint score, mean (SD)</p> <p>G1: 12.3 (5.9) G2: 11.2 (5.6)</p> <p>Percent change</p> <p>G1: -6.2 (36.9) G2: -25.0 (30.4) P = NR</p> <p>Response 50% or greater improvement, n (%)</p> <p>G1: 7 (12.1) G2: 12 (23.5) P = NS</p> <p>Remitters, less than 5, n (%)</p> <p>G1: 8 (13.8) G2: 8 (15.7) P = NS</p>	<p><i>Attrition:</i></p> <p>NA</p> <p><i>Adherence/ compliance:</i></p> <p>NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Poirier and Boyer, 1999⁵³</p> <p><i>Country, setting</i> France, Multi-center</p> <p><i>Funding</i> Wyeth-Lederle, Paris France</p> <p><i>Research Objective</i> Compare the efficacy and safety of venlafaxine and paroxetine in patients with treatment-resistant depression.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 123</p> <p><i>Duration</i> 4 weeks</p> <p><i>Interventions</i> G1: Venlafaxine G2: Paroxetine</p> <p><i>Parameters</i> G1: Venlafaxine initiated at 37.5 mg twice daily and increased to 200 - 300 mg/day G2: Paroxetine initiated at 20mg/day and increased to 30 – 40 mg/day</p> <p><i>Stable psychotropic medications allowed</i> No antipsychotics or MAOIs in last month; No anti coagulants, lithium, phenytoin, mood stabilizers or ECT. Stable anxiolytics could be continued.</p>	<p><i>TRD definition</i> • Resistance to two previous successive antidepressant treatments for current episode. • Remission defined as HAM-D17 <10</p> <p><i>Tier 1</i></p> <p><i>Setting(s)</i> Inpatient or Outpatient;</p> <p><i>Inclusion criteria</i> • Inpatient or Outpatient; 18-60 years • Major Depression < 8 months old • HAM-D, 17 score ≥ 18 • TRD</p> <p><i>Exclusion criteria</i> Use of venlafaxine or paroxetine for current episode; Hypersensitive to venlafaxine or paroxetine; Use of antipsychotics or monoamine oxidase inhibitors within previous month; Use of anticoagulants, lithium, phenytoin, mood stabilizers, or ECT; Anxiolytics could continue if taken at stable dose</p>	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i> Failed 1 or more, % 100 Failed 2 or more, % 100</p> <p>Current episode failures, mean NR</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar NR Bipolar I NR Bipolar II NR</p> <p><i>Age, mean yrs</i> G1: 42.5 G2: 44.1</p>	<p><i>HAM-D 17</i> Endpoint score, calculated G1: 13.5 [OC] G2: 14.3 [OC]</p> <p>Change, mean (SD) G1: -11.1 (8.5) [OC] G2: -10.2 (6.8) [OC] OC, P= 0.55 ITT, P = 0.70</p> <p>Average improvement NR</p> <p>Responders, n G1: 27 (44.3%) G2: 18 (29.0%) OC, P = 0.044 LOCF, P = 0.07</p> <p>emitters, n G1: 22 (36.1%) G2: 11 (17.7%) OC, P = 0.01 ITT, P = 0.02 Other</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p>	<p><i>Quality of Life</i> NA</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p> <p><i>MMSE</i> NA</p> <p><i>Attrition</i> NA</p> <p><i>Adherence/ compliance</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i> Switch</p> <p><i>Diagnosis</i> 100% MDD</p>	<p>one month prior and continued through study; Mental disorder other than affective disorder; Suicidal ideation; Organic disease known as factor in TRD; Seizure disorders; Alcohol or drug dependence; Cardiac, renal, or hepatic disease; Pregnant; Breastfeeding; Women not using acceptable form of contraception</p>	<p><i>Sex, % females</i> G1: 74 G2: 70 <i>P</i> = 0.59</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>HAM-D 17</i> Baseline n G1: 61 (LOCF), 52 (OC) G2: 62 (LOCF), 55 (OC)</p> <p><i>Baseline score, mean (SD)</i> G1: 24.6 (3.9) G2: 24.5 (4.1)</p> <p>Groups similar at baseline Yes</p>	<p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> Baseline n G1: 61 (LOCF), 52 (OC) G2: 62 (LOCF), 55 (OC) Average percentage improvement G1: 73% [OC] G2: 84% [OC] <i>P</i> = 0.39</p> <p>Proportion of patients achieving a score of 1 or 2, n (%) G1: 33 (64) [OC] G2: 36 (66) [OC] <i>P</i> = NS LOCF results “look similar”</p>	
<p><i>Author, Year</i> Shelton et al., 2005⁵⁴</p> <p><i>Country, setting</i> United States and Canada, multicenter (71 sites)</p> <p><i>Funding</i> Eli Lilly and Company</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Mixed-effects model repeated-measures regression</p> <p><i>N</i> 500</p>	<p><i>TRD definition</i> ≥ 1 past treatment failure to an SSRI after ≥ 4 weeks of therapy at a therapeutic dose. Failure was not required to be in current episode; and treatment failure during a 7 week nortriptyline dose-escalation lead-in period.</p>	<p><i>Subgroups</i> Patients with an SSRI treatment failure during the current MDD episode.</p> <p><i>Treatment Failure</i> Failed 1 or more, % 100</p> <p>Failed 2 or more, % 100</p>	<p><i>HAM-D 21</i> NR</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> Baseline n G1: 146 G2: 144 G3: 142 G4: 68</p>	<p><i>Quality of Life</i> NA</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p> <p><i>MMSE</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i></p> <p>To replicate findings within a larger patient sample, hypothesizing that olanzapine/fluoxetine combination would produce greater reductions in depressive symptoms than other treatment groups.</p> <p><i>Quality Rating</i> Good</p>	<p><i>Duration</i> 8 Weeks</p> <p><i>Interventions</i> G1Olanzapine/fluoxetine combination G2: Olanzapine monotherapy G3: Fluoxetine monotherapy G4: Nortriptyline</p> <p><i>Parameters</i> Olanzapine/fluoxetine combination = 25mg/d fluoxetine and 6mg/d olanzapine OR 50mg/d fluoxetine and 12mg/d olanzapine; Mean modal doses (SD) = 8.5 (3.1) olanzapine plus fluoxetine 35.6 (12.7)</p> <p>Olanzapine monotherapy = 6-12mg/d; Mean modal dose (SD)= 8.3(3.1)</p> <p>Fluoxetine monotherapy= 25-50mg/d; Mean modal dose (SD) = 35.8 (12.8)</p> <p>Nortriptyline = 25-175mg/d Mean modal dose (SD) = 103.5 (33.9)</p>	<p>So, 2 failed treatments (one in current episode)</p> <p>Failure defined as < 30% improvement in MADRS total score from baseline.</p> <p>Treatment response ≥ 50% decrease from baseline to endpoint in MADRS total score.</p> <p>Remission = 2 consecutive MADRS total scores ≤ 8.</p> <p><i>Tier 1</i></p> <p><i>Setting(s)</i> NR</p> <p><i>Inclusion criteria</i> Unipolar, nonpsychotic MDD</p> <p>Treatment failure as described above.</p> <p>MADRS total score ≥ 20 at both beginning and end of screening period.</p> <p><i>Exclusion criteria</i> Concomitant medication with primary central</p>	<p>Current episode failures, mean NR</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar G1100 G2:100 G3:100 G4: 100</p> <p>Bipolar I G10 G2:0 G3:0 G4: 0</p> <p>Bipolar II G10 G2:0 G3:0 G4: 0</p> <p><i>Age, mean yrs</i> G142.5 G2:43.4 G3:41.7 G4:41.5</p>	<p>Baseline score, mean (SD) G1: 28.5 (7.5) G2: 28.4 (7.3) G3: 28.4 (7.3) G4: 28.8 (6.5)</p> <p>Week 0.5 Endpoint score, calculated G1: 24.87 G2: 24.62 G3: 25.88 G4: 25.85 Change, mean (SE) G1: -3.63 (0.65) G2: -3.78 (0.65); vs. G1: P = 0.868 G3: -2.52 (0.66); vs. G1: P = 0.230 G4: -2.95 (0.94); vs. G1: P = 0.555</p> <p>Week 1 Endpoint score, calculated G1: 21.6 G2: 23.2 G3: 23.23 G4: 25.02 Change, mean (SE) G1: -6.90 (0.65) G2: -5.20 (0.65); vs. G1: P = 0.063 G3: -5.17 (0.66); vs. G1: P = 0.061 G4: -3.78 (0.95); vs. G1: P = 0.007</p>	<p><i>Attrition</i> NA</p> <p><i>Adherence/ compliance</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy Switch</i></p>	<p>nervous system activity were not allowed with the exception of lorazepam. No other benzodiazepines were permitted. Patients developing psychotic symptoms during lead-in phase. Pregnant; Lactating; ECT treatment within 1 month or likely to require ECT during the study.</p>	<p><i>Sex, % females</i> G1:67.1 G2:64.6 G3:72.5 G4: 67.6</p> <p><i>Race, % white</i> G1:90.4 G2:82.6 G3:90.8 G4: 88.2</p> <p><i>Right handed, %</i> G1:NR G2:NR G3:NR G4:NR</p> <p>Groups similar at baseline Yes</p>	<p>Week 2 Endpoint score, calculated G1: 19.51 G2: 21.42 G3: 22.72 G4: 24.10 Change, mean (SE) G1: -8.99 (0.65) G2: -6.98 (0.65); vs. G1: <i>P</i> = 0.029 G3: -5.68 (0.66); vs. G1: <i>P</i> < 0.001 G4: -4.70 (0.95); vs. G1: <i>P</i> < 0.001</p> <p>Week 3 Endpoint score, calculated G1: 19.28 G2: 20.85 G3: 22.30 G4: 23.47 Change, mean (SE) G1: -9.22 (0.65) G2: -7.55 (0.66); vs. G1: <i>P</i> =0.071 G3: -6.10 (0.67); vs. G1: <i>P</i> < 0.001 G4: -5.33 (0.95); vs. G1: <i>P</i> < 0.001</p> <p>Week 4 Endpoint score, calculated G1: 18.56 G2: 20.54</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G3: 21.56 G4: 22.84</p> <p>Change, mean (SD) G1: -9.94 (0.66) G2: -7.86 (0.66); vs. G1: <i>P</i> = 0.026 G3: -6.84 (0.68); vs. G1: <i>P</i> = 0.001 G4: -5.96 (0.95); vs. G1: <i>P</i> < 0.001</p> <p>Week 5 Endpoint score, calculated G1: 19.50 G2: 21.18 G3: 21.27 G4: 21.33</p> <p>Change, mean (SE) G1: -9.00 (0.67) G2: -7.22 (0.67); vs. G1: <i>P</i> = 0.061 G3: -7.13 (0.68); vs. G1: <i>P</i> = 0.050 G4: -7.47 (0.95); vs. G1: <i>P</i> = 0.190</p> <p>Week 6 Endpoint score, calculated G1: 19.14 G2: 21.00 G3: 20.31 G4: 20.25</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Change, mean (SE) G1: -9.36 (0.68) G2: -7.40 (0.69); vs. G1: P = 0.043 G3: -8.09 (0.69); vs. G1: P = 0.191 G4: -8.55 (0.96); vs. G1: P = 0.491</p> <p>Week 7 Endpoint score, calculated G1: 19.59 G2: 21.54 G3: 20.49 G4: 20.18</p> <p>Change, mean (SE) G1: -8.91 (0.69) G2: -6.86 (0.70); vs. G1: P = 0.036 G3: -7.91 (0.70); vs. G1: P = 0.305 G4: -8.62 (0.97); vs. G1: P = 0.805</p> <p>Week 8 Endpoint score, calculated G1: 19.79 G2: 21.45 G3: 19.89 G4: 21.34 Change, mean (SE) G1: -8.71 (0.70) G2: -6.95 (0.71); vs. G1: P = 0.77 G3: -8.51 (0.70); vs. G1:</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>$P = 0.841$ G4: -7.46 (0.98); vs. G1: $P = 0.298$</p> <p>Average percentage improvement NR</p> <p>Responders, n [calculated] (% as reported in text) G1: 40 (27.5) G2: 27 (19.3) G3: 41 (28.9) G4: 20 (30.3) $P = 0.18$</p> <p>Remitters, n [calculated] (% as reported in text) G1: 24 (16.9) G2: 18 (12.9) G3: 18 (13.3) G4: 12 (18.2) $P = 0.62$ ** Of the 72 pts who remitted, 7 relapsed; No significant difference between groups $P = 0.21$</p> <p>Other: Post hoc Subgroup Analysis of pts with treatment failure during current MDD episode N=314</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Significant main effects for treatment ($P = 0.004$), for visit ($P < 0.001$), and for treatment-by-visit interaction ($P = 0.04$).</p> <p><i>Endpoint score, calculated</i> G1: 119.4 G2: 22.8 G3: 21.3 G4: 20.9</p> <p><i>Change, mean</i> G1: -9.1 G2: -5.6; vs. G1: $P = 0.005$ G3: -7.1; vs. G1: $P = 0.18$ G4: -7.9; vs. G1: $P = 0.33$</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> Baseline n G1: 146 G2: 144 G3: 142 G4: 68</p> <p>Baseline score, mean (SE) G1: 4.4 (0.1) G2: 4.3 (0.1)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G3: 4.3 (0.1) G4: 4.4 (0.1)</p> <p>Endpoint score, calculated G1: 3.4 G2: 3.7 G3: 3.6 G4: 3.7</p> <p>Change, mean (SE) G1: -1.0 (0.1) G2: -0.6 (0.1) G3: -0.7 (0.1) G4: -0.7 (0.1)</p> <p>P-Values: Overall: $P = 0.048$ G1: vs. G2: $P = 0.006$ G1: vs. G3: $P = 0.088$ G1: vs. G4: $P = 0.131$</p> <p>CGI-I NR</p>	
<p><i>Author, Year</i> Shelton et al., 2005⁵⁴</p> <p><i>Country, setting</i> NR, outpatient setting</p> <p><i>Funding</i> NR</p> <p><i>Research Objective:</i> To assess the efficacy and safety of olanzapine combined with</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> = 28</p> <p><i>Duration</i></p> <p>8 weeks</p> <p><i>Interventions</i> G1: Olanzapine + placebo (OLA) G2: Fluoxetine +</p>	<p><i>TRD definition</i> Failure "...history of failure to respond to antidepressants of two different classes, one of which was not an SSRI, after at least 4 weeks of therapy at an acceptable therapeutic dose. Failure to respond was confirmed prospectively during a screening period in</p>	<p><i>Subgroups</i> - None</p> <p><i>Treatment Failure</i> Failed 1 or more, 100% Failed 2 or more, 100%</p> <p>Current episode failures, mean NR</p> <p>Mean failed trials</p> <p>Previous treatment, not specified, 0%</p>	<p><i>HAM-D 21</i> Change, mean (SD) G1: -5.9 G2: -3.8 G3: -11.7 G3 vs. G1, $P = 0.03$ G3 vs. G2 ($P = 0.07$)</p> <p><i>MADRS</i> Baseline n G1: 8 G2: 10 G3: 10</p>	<p><i>Quality of Life:</i> NA</p> <p><i>Adverse Events:</i> NA</p> <p><i>Neuropsychological or executive functioning:</i> NA</p> <p><i>MMSE:</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>fluoxetine versus either agent alone in patients with recurrent major depressive disorder who were unresponsive to conventional antidepressant therapy.</p> <p><i>Quality Rating – Good</i></p>	<p>placebo (FLU) G3: Olanzapine + fluoxetine (COMBO)</p> <p><i>Parameters</i> G1: Olanzapine + placebo (OLA): 5-20 mg/d G2: Fluoxetine + placebo (FLU): 20-60mg/d G3: Olanzapine + fluoxetine (COMBO): same dose as above</p> <p><i>Strategy –</i> Augment (add OLA to FLU) or switch (to OLA)</p>	<p>which fluoxetine was given.”; ≥ 2</p> <p><i>Tier 1</i></p> <p><i>Setting(s)</i> Outpatient</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Met DSM-IV criteria for recurrent major depression without psychotic features • Resistant to conventional antidepressant pharmacotherapy • Score of greater to or equal to 20 on the HRSD-21 <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • History of psychosis, dysthymic disorder, or bipolar disorder 	<p><i>Polarity, %</i> Unipolar 100%</p> <p><i>Age, mean yrs - 42:</i></p> <p><i>Sex, % females - 75</i></p> <p><i>Race, % white - 96</i></p> <p>Groups similar at baseline Unclear; only #'s are reported</p> <p><i>HAM-D 21</i></p> <p>Baseline n G1: (OLA): 8 G2 (FLU): 10 G3 (COMBO):10 Mean baseline severity not reported, but eligibility criteria required that 21-item HAM-D was ≥ 20,</p>	<p>Change, mean (SD) G1: -2.8 G2: -1.2 G3:-13.6</p> <p>Responders, n (%) G1: 0 (0) G2: 1 (10) G3:6 (60) G3 vs. G1, <i>P</i> = 0.03 G3vs. G2, <i>P</i> = 0.11</p>	<p><i>Attrition:</i> NA</p> <p><i>Adherence/ compliance:</i> NA</p>
<p><i>Author, Year</i> Thase, 2007⁵⁵</p> <p><i>Country, setting</i> United States and Canada</p> <p><i>Funding</i> Eli Lilly and Co.</p>	<p><i>Study design</i> RCT; 2 identical concurrent studies; sites were randomly assigned to either Study 1 or Study 2.</p> <p><i>Type of analysis</i> ITT</p>	<p><i>TRD definition</i> “Failure to achieve satisfactory response to an antidepressant (except fluoxetine) after at least 6 weeks at a therapeutic dose occurring within the current episode of MDD.” Second failure occurred during, “an 8-</p>	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i> Failed 1 or more, % 100%</p> <p>Failed 2 or more, % 100%</p>	<p><i>HAM-D 21</i> NR</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> Baseline n (both studies combined) G1: 200 G2: 206 G3:200</p>	<p><i>Quality of Life</i> NA</p> <p><i>Adverse Events</i> NA</p> <p><i>Neuropsychological or executive functioning</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i></p> <p>Examine the efficacy and tolerability of olanzapine/fluoxetine combination, olanzapine and fluoxetine in outpatients with 2 treatment failures during the current mood episode.</p> <p><i>Quality Rating</i></p> <p>Fair</p>	<p>N 605</p> <p><i>Duration</i> 8 weeks</p> <p><i>Interventions</i> G1: Olanzapine/Fluoxetine Combination G2:Fluoxetine G3: Olanzapine</p> <p><i>Parameters</i> G1: Olanzapine 6, 12, or 18 mg/day + 50 mg/day fluoxetine G2: Olanzapine 6, 12, or 18 mg/day G3: Fluoxetine 50 mg/day</p> <p><i>Strategy</i> Switch</p>	<p>week open-label lead-in phase to establish fluoxetine resistance.”</p> <p><i>Setting(s)</i> Outpatient</p> <p><i>Inclusion criteria</i> 18-65 years; HAM-D17 \geq 22; Diagnosis of MDD, recurrent, without psychotic features; Failure to 6 week antidepressant therapy within current episode of MDD; Failure to exhibit response to fluoxetine during 8 week lead-in phase.</p> <p><i>Exclusion criteria</i> Schizophrenia; Schizoaffective disorder; Psychotic disorders, Bipolar disorder; Posttraumatic stress disorder; Dissociative disorders; Pregnant; Breastfeeding; Postpartum depression; MDD with atypical features; MDD with seasonal pattern; Paranoid, schizoid, schizotypal, antisocial, severe borderline personality disorder; Significant medical</p>	<p>Current episode failures, mean NR</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar G1:100% G2:100% G3:100% Bipolar I G2: 0 G3: 0 Bipolar II G1: 0 G2: 0 G3:0</p> <p><i>Age, mean yrs</i> Study 1 G1: 43.3 G2: 44.8 G3: 45.7</p> <p>Study 2 G1: 45.3 G2: 44.5 G3: 43.0</p>	<p>Study1 Baseline score, mean (SD) G1: 29.5 (7.1) G2: 29.7 (6.9) G3: 29.7 (7.1)</p> <p>Study 2 Baseline score, mean (SD) G1: 30.6 (6.1) G2: 30.1 (5.9) G3: 30.1 (6.3)</p> <p>Pooled Baseline score, mean (SD) G1: 30.0 (6.7) G2: 29.9 (6.4) G3: 29.9 (6.7)</p> <p>Study1 Endpoint score, calculated G1: 18.7 G2: 20.3 G3: 19.6</p> <p>Study2 Endpoint score, calculated G1: 16.0 G2: 21.1 G3: 22.4</p> <p>Pooled Endpoint score, calculated</p>	<p><i>MMSE</i> NA</p> <p><i>Attrition</i> NA</p> <p><i>Adherence/ compliance</i> NA</p>

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		illness; Concomitant medications with primary central nervous system activity Interim Exclusion Criteria: Response to fluoxetine during lead in prior to randomization or presentation of psychotic features.	Pooled G1: 44.3 G2: 44.6 G3: 44.3 <i>Sex, % females</i> Study 1 G1: 61.8 G2: 58.7 G3: 58.3 Study 2 G1: 70.4 G2: 65.7 G3: 65.0 Pooled G1: 66.0 G2: 62.1 G3: 61.8 <i>Race, % white</i> Study 1 G1: 85.3 G2: 83.7 G3: 76.0 Study 2 G1: 91.8 G2: 88.2 G3: 88.3 Pooled G1: 88.5 G2: 85.9 G3: 82.4 <i>Right handed, %</i> G1: NR	G1: 17.4 G2: 20.7 G3: 21 Study 1 Change, mean (SD) G1: -10.8 (10.0) G2: -9.4 (9.9) G3: -10.1 (9.6) P-values: Overall, $P = 0.640$ G1: vs. G2, $P = 0.346$ G1: vs. G3, $P = 0.624$ Study 2 Change, mean (SD) G1: -14.6 (10.2) G2: -9.0 (9.5) G3: -7.7 (8.2) P-values: Overall, $P < 0.001$ G1: vs. G2, $P < 0.001$ G1: vs. G3, $P < 0.001$ Pooled Change, mean (SD) G1: -12.6 (10.3) G2: -9.2 (9.7) G3: -8.9 (9.0) P-values: Overall, $P < 0.001$ G1: vs. G2, $P < 0.001$ G1: vs. G3, $P < 0.001$ Study 1 Responders, n (%) G1: 37 (36.6) G2: 30 (29.4)	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
			<p>G2: NR G3:NR</p> <p>Groups similar at baseline</p> <p>Yes</p> <p><i>Tier</i></p> <p>Tier 1</p>	<p>G3: 34 (35.8) Overall <i>P</i> = 0.496</p> <p>Study 2 Responders, n (%) G1: 43 (44.3) G2: 30 (29.7) G3: 17 (16.7) Overall <i>P</i> <0.001</p> <p>Pooled Responders, n (%) G1: 80 (40.4) G2: 60 (29.6) G3: 51 (25.9) Overall <i>P</i> = 0.006 G1: vs. G2, <i>P</i> = 0.028 G1: vs. G3, <i>P</i> = 0.003</p> <p>Study1 Remitters, n (%) G1: 24 (23.8) G2: 18 (17.6) G3: 18 (18.9) Overall <i>P</i> = 0.522</p> <p>Study 2 Remitters, n (%) G1: 30 (30.9) G2: 16 (15.8) G3: 11 (10.8) Overall <i>P</i> = 0.001</p> <p>Pooled Remitters, n (%) G1: 54 (27.3) G2: 34 (16.7) G3: 29 (14.7)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Overall $P = 0.004$ G1: vs. G2, $P = 0.012$ G1: vs. G3, $P = 0.003$</p> <p>Other</p> <p>IDS</p> <p>CGI-S Baseline n (both studies combined) G1: 200 G2: 206 G3:199</p> <p>Study 1 Baseline score, mean (SD) G1: 4.5 (0.7) G2: 4.7 (0.7) G3: 4.6 (0.7)</p> <p>Study 2 Baseline score, mean (SD) G1: 4.7 (0.7) G2: 4.7 (0.7) G3: 4.7 (0.7)</p> <p>Pooled Baseline score, mean (SD) G1: 4.6 (0.7) G2: 4.7 (0.7) G3: 4.7 (0.7)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Study 1 Endpoint score, calculated G1: 3.4 G2: 3.7 G3: 3.5</p> <p>Study 2 Endpoint score, calculated G1: 3.2 G2: 3.6 G3: 3.9</p> <p>Pooled Endpoint score, mean (SD) G1: 3.3 G2: 3.7 G3: 3.8</p> <p>Study 1 Change, mean (SD) G1: -1.1 (1.3) G2: -1.0 (1.2) G3: -1.1 (1.1) Overall, $P = 0.681$ G1: vs. G2, $P = 0.384$ G1: vs. G3, $P = 0.722$</p> <p>Study 2 Change, mean (SD) G1: -1.5 (1.3) G2: -1.1 (1.2) G3: -0.8 (1.1) Overall, $P < 0.001$ G1: vs. G2, $P = 0.004$ G1: vs. G3, $P < 0.001$</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Pooled Change, mean (SD) G1: -1.3 (1.4) G2: -1.0 (1.2) G3: -0.9 (1.1) Overall, $P = 0.003$ G1: vs. G2, $P = 0.008$ G1: vs. G3, $P = 0.001$</p> <p><i>CGI-I</i> NR</p> <p><i>Brief Psychiatric Rating Scale (BPRS)</i></p> <p>Baseline n (both studies combined) G1: 200 G2: 206 G3: 199</p> <p>Study 1 Baseline score, mean (SD) G1: 17.1 (7.7) G2: 17.6 (7.7) G3: 16.1 (6.5)</p> <p>Study 2 Baseline score, mean (SD) G1: 15.2 (5.7) G2: 15.3 (5.6) G3: 14.8 (5.5)</p> <p>Pooled Baseline score, mean (SD)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G1: 16.2 (6.8) G2: 16.5 (6.8) G3: 15.4 (6.0)</p> <p>Study 1 Endpoint score, calculated G1: 11.7 G2: 12.8 G3: 11.8</p> <p>Study 2 Endpoint score, calculated G1: 9.3 G2: 11.0 G3: 12.4</p> <p>Pooled Endpoint score, calculated G1: 10.6 G2: 11.9 G3: 12.1</p> <p>Study 1 Change, mean (SD) G1: -5.4 (7.5) G2: -4.8 (7.7) G3: -4.3 (7.4) Overall, <i>P</i> = 0.646 G1: vs. G2, <i>P</i> = 0.562 G1: vs. G3, <i>P</i> = 0.357</p> <p>Study 2 Change, mean (SD) G1: -5.9 (6.8) G2: -4.3 (6.1) G3: -2.4 (6.2)</p>	

Evidence Table 8. KQ1 pharm versus pharm: Tier 1 (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Overall, $P = 0.001$ G1: vs. G2, $P = 0.058$ G1: vs. G3, $P < 0.001$ Pooled Change, mean (SD) G1: -5.6 (7.2) G2: -4.6 (7.0) G3: -3.3 (6.8) Overall, $P = 0.009$ G1: vs. G2, $P = 0.097$ G1: vs. G3, $P = 0.002$	

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰ Avery 2007¹¹</p> <p><i>Country, setting</i> USA, Single center, University department of psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good</p> <p>Fair for KQ2 and subgroups¹¹ (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint Interventions G1: High-left rTMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazepines G1: 26% vs. G2: 24%)</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥3 on ATHF) • Failures not required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous rTMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence within past 2 years,</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p><i>Baseline n</i> G1: 35 G2: 33</p> <p><i>Treatment Failure</i> Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67) Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100 Age, mean yrs G1: 44.3 G2: 44.2 Sex, % females G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p> <p>Groups similar at baseline Yes</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 15.7 G2: 19.8 Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time <i>P</i> = 0.002</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) <i>P</i> = 0.008</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) <i>P</i> = 0.033</p> <p><i>HAM-D 17</i> 6- month relapse, n (%) G1: 6 (54.5); 1 lost to follow up G2: 1 (50); 1 lost to follow up <i>P</i> = NR</p> <p><i>G1</i></p> <p><i>G2:BDI</i> Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33).</p> <p>The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, <i>P</i> < 0.001).</p> <p>Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi- square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms. (Data = NR)</p>

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> • Identical stimulation parameters • Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> • antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity 	<p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>	<p>Random Regression analyses revealed significant group by time interaction ($P = 0.003$)</p>	<p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$)</p> <p>No statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures. models were refit without interaction term, there was no significant treatment group main effect ($P > 0.05$) evident for any of neuropsychological tests, indicating groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant improvement in individual neuropsychological test</p>

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>performances for both groups.</p> <p>No confusion was associated with TMS treatments. GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session.</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR</p> <p>Very unclear as to when patients discontinued</p>

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Boutros et al., 2002¹³</p> <p><i>Country, setting</i> US, Yale School of Medicine and VA-Connecticut, outpatient</p> <p><i>Funding</i> VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer</p> <p><i>Research Objective</i> To provide additional data on efficacy and safety for rTMS as an augment strategy in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 21</p> <p><i>Duration</i> 2 weeks txt; follow-up with responders for up to 20 weeks post txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts allowed to continue all current psychotropic meds</p> <p><i>Strategy</i> Augmentation, 3 pts in active and 1 in sham txt were not on any meds</p> <p><i>Parameters</i> rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 58</p>	<p><i>TRD definition</i> • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major Depression • HAM-D25 >= 20</p> <p><i>Exclusion criteria</i> • Suicidality • "Prominent" psychotic symptoms • History of neurological disorders • current drug abuse</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 49.5 G2: 52.0</p> <p><i>Sex, % females</i> G1: 25 G2: 10</p> <p><i>Right handed, %</i> G1: 90.9 G2: 88.9</p> <p><i>HAM-D</i> Baseline n G1: 12 G2: 9 Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)</p>	<p><i>HAM-D 25</i> Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11 Change, mean (SD) G1: -11.75 G2: -6.22 P = NS</p> <p><i>Responders, n</i> Defined as 30% improvement on Ham-D 25 G1: 7 G2: 2</p> <p><i>Responders, n (%)</i> Defined as 50% improvement on Ham-D 25 G1: 3 G2: 2</p> <p><i>Relapse</i> Defined as ≥ baseline score ± 10% Of 6 active treatment responders included in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in</p>	<p><i>Adherence/ compliance</i> NR</p> <p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6</p> <p><i>Cognitive impairment, %</i> Difficulty concentrating (phase 1 only) G1: 25 G2: NR</p> <p><i>Headache, %</i> "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR</p> <p><i>Attrition</i> Overall, % 18.2% (4/22) At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10)</p> <p><i>At end of follow-up, %</i> NR</p>

Evidence Table 9. KQ 2 – Tier 1: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: <ul style="list-style-type: none"> • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp 			the 20-week follow-up, 1 relapsed.	Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR <i>Adherence/ compliance</i> NR

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Berman et al., 2000²⁸</p> <p><i>Country, setting</i> US, urban community health center, inpatient and outpatients</p> <p><i>Funding</i> Veterans Administration, NIMH, State of CT</p> <p><i>Research Objective</i> To assess efficacy of rTMS in unmedicated TRD patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> 2 weeks (10 weekdays of txt)</p> <p><i>Primary outcome =</i> HAM-D 25 at 2 wks</p> <p><i>Interventions</i> G1: rTMS G2: Sham rTMS</p> <p><i>Medications Allowed</i> All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS – LDLPFC • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 58</p>	<p><i>TRD definition</i> • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imipramine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Current Major depressive episode (per HAM-D)</p> <p><i>Exclusion criteria</i> • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control</p>	<p><i>Treatment Failure</i> Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 augmentation in each group)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 90 Bipolar II G1: 0 G2: 10 Age, mean yrs G1: 45.2 G2: 39.4 Sex, % females G1: 20 G2: 40 Race, % white G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic)</p> <p><i>HAM-D 25</i> Baseline n G1: 10 G2: 10 Baseline score, mean (SD) G1: 37.1 G2: 37.3</p>	<p>HAM-D 25 G1: rTMS G2: Sham TMS</p> <p>Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4 *Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) P < 0.05 Responders, n 50% decrease from baseline and score ≤ 15 G1: 1 (10) G2: 0 P = 0.09</p> <p>2-month maintained response, n % G1: 1 (100) G2: 0 (100) P=NR</p> <p>Three partial responders symptom severity returned to baseline within 1-2 weeks BDI Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) P = 0.27</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, n G1: 60 G2: 50</p> <p>Difficulty starting urination great in active group P = 0.03</p> <p>Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR)</p> <p>Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appetite, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Pulses per session:800 • Total number of sessions: 10 in 10 days <p>Sham</p> <ul style="list-style-type: none"> • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp 				<p>coordination, and muscle stiffness</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 15 At end of treatment, % G1: 0.0 G2: 30.0 At end of follow-up, % G1: NA G2: NA Withdrawals due to efficacy, % G1: 0 G2: 30 Withdrawals due to adverse events, % G1: 0 G2: 0</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> O'Reardon, 2007³¹ Janicak, 2007^{56*} Sovason, 2007⁵⁷ Janicak 2010⁵⁸</p> <p><i>Country, setting</i> US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported</p> <p><i>Funding</i> Neuronetics</p> <p><i>Research Objective</i> To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral prefrontal cortex is effective and safe in acute treatment of major depression and to determine whether the benefit of TMS dissipates over a clinically meaningful duration of follow-up</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 325 randomized; Continuation of 67 responders from original 301 patients included in final analysis; 99 with rTMS response compared with 21 sham responders in durability study</p> <p><i>Duration</i> 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over after 4 weeks if not responding. 24 weeks; open-label continuation of effect study Interventions G1: Active TMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use</p>	<p><i>TRD definition</i> • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime</p> <p><i>Tier 2 Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i> • Aged 18–70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed at screening assessment</p> <p><i>Exclusion criteria</i> • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder</p>	<p>Baseline N (Continuation Study) G1: 165 (44) G2: 160 (23) Current episode failures, mean G1: 1.6 G2: 1.6</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar 100 Age, mean yrs (Continuation Study) G1: 47.9 (49.2) G2: 48.7 (48.6) Sex, % females (Continuation Study) G1: 55.5% (54.5%) G2: 50.7% (47.8%) Race, % white (Continuation Study) G1: 94.2% (88.6%) G2: 89.7% (82.6%)</p> <p><i>HAM-D 17</i> Baseline score, mean (SD); Continuation Study G1: 22.6 (3.3); 6.5 (4.8) G2: 22.9 (3.5); 7.5(5.0)</p>	<p><i>HAM-D 17</i> Analyzed n (Continuation study) G1: 155 (37) G2: 146 (19)</p> <p>Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5) At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0)</p> <p>Change, mean (SD) At week 2 G1: -5.2 G2: -3.5 At week 4 (Continuation Study) G1: -14.6 (6.16) G2: -14.4 (6.11) At week 6 G1: -5.5 G2: -3.3</p> <p><i>P</i> = 0.005 At week 24 (Continuation Study) G1: -15.4(6.11) G2: -17.3 (5.07)</p>	<p><i>Quality of Life</i> Medical Outcomes Study Short Form-36 (MOS SF-36) Baseline n G1: 155 G2: 146</p> <p>Baseline score, mean (SD) Mental Component Score G1: 20.4 (8.05) G2: 20.4 (7.76)</p> <p>Physical Component Score G1: 50.5 (11.01) G2: 48.8 (10.35)</p> <p>Endpoint Score NR</p> <p>Change, mean (SD) Mental Component Score At week 4 G1: 4.5 (10.16) G2: 2.0 (9.42) <i>P</i> = 0.019 At week 6 G1: 5.7 (12.65) G2: 2.9 (10.6) <i>P</i> = 0.032</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>hypnotics, anxiolytics for txt emergent insomnia or anxiety</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks; For add-on rescue treatment 2/week for 2wks then 5/week for 4wks <p>rTMS Sham:</p> <ul style="list-style-type: none"> • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil 	<ul style="list-style-type: none"> • Posttraumatic stress disorder and eating disorders (if present in past year) • Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head 	<p><i>MADRS</i> Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 32.8 (6.0); 9.0(8.2) G2: 33.9 (5.7); 10.9(8.1)</p> <p><i>IDS</i> Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 42.0 (9.4); 14.4(9.8) G2: 43.4 (9.9); 13.4(9.4)</p> <p>CGI-S Baseline n (Continuation Study) G1: 155 (44) G2: 146 (23) Baseline score, mean (SD); Continuation Study G1: 4.7 (.6); 1.9(1.2) G2: 4.7 (.7); 2.3(1.0)</p>	<p>Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9) <i>P</i> > 0.10</p> <p>At week 4 G1: 32 (20.6) G2: 17 (11.5) <i>P</i> < 0.05</p> <p>At week 4 (continuation study) G1: 30(68.2) G2: 13 (56.5)</p> <p>At week 6 G1: 38 (24.5) G2: 20 (13.7) <i>P</i> < 0.05</p> <p>At week 24 (continuation study) G1: 24(54.5) G2: 12(52.5)</p> <p>Remission rate n (%) HAM-D17 < 8 At week 2 G1: 5 (3.2) G2: 3 (2.1) <i>P</i> > 0.10</p> <p>At week 4 G1: 110 (7.1) G2: 9 (6.2) <i>P</i> > 0.10</p>	<p>Physical Component</p> <p>At week 4 G1: 0.3 (7.52) G2: 0.2 (7.28) <i>P</i> = 0.892</p> <p>At week 6 G1: 0.1 (7.49) G2: -0.2 (7.23) <i>P</i> = 0.682</p> <p>Quality of Life, Enjoyment and Satisfaction Questionnaire –Short Form (Q-LES-Q)</p> <p>Baseline n G1: 155 G2: 146 Baseline score, mean (SD) G1: 37.8 (8.23) G2: 36.5 (7.87)</p> <p>Endpoint score, mean (SD) At week 4 G1: 41.4 (10.32) G2: 39.0 (9.78)</p> <p>At week 6 G1: 42.2 (12.28) G2: 39.0 (10.15)</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At week 4 (continuation study) G1: 19(43.2) G2: 10(43.5)</p> <p>At week 6 G1: 24 (15.5) G2: 13 (8.9) <i>P</i> = 0.065</p> <p>At week 24 (Continuation Study) G1: 18 (40.9) G2: 10(43.5)</p> <p>MADRS Endpoint score, mean (SD) At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1)</p> <p>At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8)</p> <p>Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1</p> <p>At 4 weeks (Continuation Study) G1: -21.2 (10.42) G2: -20.2(10.43) At 6 weeks G1: 6 G2: 3.9</p>	<p>Change, mean (SD) At week 4 G1: 3.50 (9.19) G2: 3.80 (11.58) At week 6 G1: 2.0 (9.24) G2: 1.3 (9.85)</p> <p>Other Active rTMS vs. Sham <i>P</i> = 0.035 at week 6</p> <p><i>Adverse Events</i> Serious adverse events G1: 6 G2: 5</p> <p>Suicidality, % G1: 0.6 G 2: 1.9</p> <p>Exacerbation of depression, % Active TMS: 0.6 Sham TMS: 1.9%</p> <p>Eye pain: active, % TMS: 6.1 Sham TMS: 1.9%;</p> <p>GI disorders toothache, % Active TMS: 7.3 Sham TMS: 0.6</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At week 24 (Continuation Study) G1: -23(9.27) G2: -24.6(8.81)</p> <p>Response rate, % At week 2 G1: 8.4 G2: 6.2 <i>P</i> > 0.10</p> <p>At week 4 G1: 18.1 G2: 11.0 <i>P</i> <0.05</p> <p>At week 4 (Continuation Study) G1: 29(65.9) G2: 12 (25.2)</p> <p>At week 6 G1: 23.9 G2: 12.3 <i>P</i> <0.01</p> <p>At week 24 (continuation study) G1: 24 (54.5) G2: 11(47.8)</p> <p>Remission rate, % Remission defined as total score <10 At week 2 G1: 3.9 G2: 2.1 <i>P</i> > 0.10</p>	<p>Application site discomfort, % TMS: 10.9 Sham: 1.3%</p> <p>Application site pain, %: TMS: 35.8 Sham: 3.8</p> <p>Facial pain, % Active TMS: 6.7 Sham TMS: 3.2</p> <p>Muscle twitching, % TMS: 20.6 Sham: 3.2</p> <p>Pain of skin, % TMS: 8.5 TMS: 0.6%</p> <p>Adverse Events (Continuation Study) Constipation: G1: 0 G2: 0 Dry Mouth: G1: 0 G2: 0</p> <p>Application Site Pain: G1: 6.8%G2: 26.1%</p> <p>Arthralgia: G1: = 2.3%, G2 = 0</p> <p>Muscle Twitching: G1: = 4.5%, G2 = 13.0% Headache: G1: = 6.8%, G2 = 8.7%</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At week 4 G1: 7.1 G2: 6.2 $P > 0.10$ At week 4 (Continuation Study) G1: 20(45.5) G2: 11(47.8) At week 6 G1: 14.2 G2: 5.5 $P < 0.05$ At week 24 (continuation study) G1: 18(40.1) G2:9(39.1) Other Relapse Rates: Relapse defined as recurrence of MDD per DSM-IV ≥ 2 weeks (HAM-D 17 ≥ 20; CGI-S ≥ 4) At week 4 (continuation study) G1: 2.3% G2: 7.8% At week 24 (continuation study) G1: 7.8% G2: 15.0%</p>	<p>Insomnia: G1: 0 G2: 0 MMSE NR <i>Attrition</i> Overall, % 15 At end of treatment, % G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6% At end of follow-up, % NR Withdrawals due to efficacy, % G1: 0.6% G2: 1% Withdrawals due to adverse events, % G1: 5% G2: 4% Other 325 subjects were randomized 24 were "nonevaluable" 301 continued to receive at least 1 treatment, these 301 were included in final analysis 277 completed study through week 4.</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Symptomatic Worsening (% experiencing worsening) G1: 36.4% G2: 47.8% Kaplan-Meier Survival estimate of symptomatic deterioration G1: 37.4% G2: 60.8% In durability study combining rTMS responders Relapse, n (%) G1: 10 (10) G2: 3 (13.6)	<i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Stern et al., 2007³²</p> <p><i>Country, setting</i> NR, outpatient setting</p> <p><i>Funding</i> The Milton Fund, NARSAD, Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Ciencia</p> <p><i>Research Objective</i> To test hypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in the analysis</p> <p><i>N</i> 45</p> <p><i>Duration</i> • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse.</p>	<p><i>TRD definition</i> • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20</p> <p><i>Exclusion criteria</i> • H/O any psychotic disorder (incl. schizophrenia or</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100 % MDD</p> <p><i>Age, mean yrs</i> G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3</p> <p><i>Sex, % females</i> G1: 60 G2: 60 G3: 70 G4: 60</p> <p><i>Right handed, %</i> 100</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5) At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6) Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> 9/45 pts reported severe headaches (pts by group NR); no seizures</p> <p><i>Attrition</i> Overall, %: 17.8 At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10 At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an</p> <p><i>Quality Rating</i> Fair</p>	<p>Primary Outcome: HAM-D at 2 weeks and 2 weeks after treatment Interventions G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz rTMS to right DLPFC G4: Sham rTMS</p> <p><i>Medications allowed</i> No psychotropic medications were allowed</p> <p><i>Parameters</i> rTMS High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days</p> <p>Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1</p>	<p>schizoaffective disorder)</p> <ul style="list-style-type: none"> • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy 	<p><i>HAM-D 21</i> Baseline n G1: 10 G2: 10 G3: 10 G4: 15 Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)</p>	<p>Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3)</p> <p>Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, $P = 0.001$</p> <p>2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, $P = 0.00001$</p> <p>Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0 At week 2 G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p>	<p>Withdrawals due to efficacy: NR Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20</p> <p>Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period. Reported in text as dropped out following week 2.</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Sham rTMS: • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above <i>Strategy Switch</i> 			<p>1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>Remitters, n HAM-D ≤ 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%) G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%)</p> <p>1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%)</p>	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 <i>P</i> = NS (all times); G2 vs. G4 and G1: vs. G3 <i>P</i> = NS (all times)	
<p><i>Author, Year</i> Bortolomasi et al., 2006³⁴</p> <p><i>Country, setting</i> Italy, single center, inpatient vs. outpatient NR</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To investigate outcome of depressed patients treated for 1 month with high frequency rTMS on left frontal lobe at long time periods</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in analysis</p> <p><i>N</i> 19</p> <p><i>Duration</i> Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • Drug resistance (not defined) • Not required or not specified to be in current episode <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps 	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i></p> <p>Unipolar G1: 83.3 G2: 85.7</p> <p>Bipolar G1: 16.7 G2: 14.3</p> <p>Age, mean yrs G1: range 45-56 G2: range 44-53 Overall: 55.6</p> <p>Sex, % females G1: 58 G2: 57</p> <p><i>Race, % white</i> NR</p>	<p><i>HAM-D 24</i></p> <p>Endpoint score, mean (SD)</p> <p>At week 1 G1: 11.33</p> <p>G2: 18.29 At week 4 G1: 11.42</p> <p>G2: 19.14</p> <p>At week 12 NR</p> <p>Change, mean (SD) At week 1 G1: -13.84 G2: NR <i>P</i> = NR, significant</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No adverse effects were reported in either group, except for mild cephalgia by 3 patients treated with anti-inflammatory drugs</p> <p>Headache, %</p> <ul style="list-style-type: none"> • 3 patients reported mild headaches after treatment • All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Medications allowed</i> Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry)</p> <p><i>Strategy</i> Augmentation Allowed to continue on failed SSRIs (63.2%) and TCAs (26.3%), No meds (5.3%)</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil <p>Sham</p> <ul style="list-style-type: none"> • Stimulation coil was placed perpendicular to the scalp surface without direct contact. Coil position was fixed for all TMS sessions, 		<p><i>Right handed, %</i> Overall: 100</p> <p>Groups similar at baseline Yes</p> <p><i>Tier</i></p> <p><i>HAM-D 24</i> Baseline n G1: 12 G2: 7 Baseline score, mean (SD) G1: 25.17 G2: NR</p>	<p>Group x time at wk 2 and 4, $P < 0.05$ At week 4 G1: -13.75 G2: NR</p> <p>At week 12 NR IG1: rTMS G2: Sham Baseline n G1: 12 G2: 7 Baseline score, mean (SD) G1: 25.42 G2: NR</p> <p>Endpoint score, mean (SD) At week 1 G1: 12.25 G2: 22.43 At week 4 G1: 11.67 G2: 24.57</p> <p>Change, mean (SD) At week 1 G1: 13.17 G2: NR At week 4 G1: 13.75 G2: NR</p>	<p>after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep.</p> <ul style="list-style-type: none"> • 3 patients reported mild headaches after treatment <p><i>Attrition</i> NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	and stimulation at this site evoked minimal motor activity				
<p><i>Author, Year</i> McLoughlin et al., 2007⁷ Eranti et al., 2007⁸ Knapp et al., 2008⁹</p> <p><i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital in Invicta Mental Health Trust in Kent, 65.2% were inpatients</p> <p><i>Funding</i> National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters)</p> <p><i>Type of analysis</i> m-ITT</p> <p><i>N</i> 46</p> <p><i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p> <p><i>G1: ECT</i> <i>G2: rTMS</i></p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> All patients referred for ECT: No failure required <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Right handed patients more than 18 years old referred for ECT due to major depressive episode <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Inability to have rTMS because of metallic implants or foreign bodies History of seizures Substance misuse in previous 6 months Being medically unfit for general anesthesia or ECT: ECT or rTMS in previous 6 months, Dementia or other axis I diagnosis Inability or refusal to provide informed consent. 	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % Age, mean yrs G1: 63.6 G2: 68.3 Sex, % females G1: 67.7 G2: 72.7</p> <p><i>Right handed, %</i> Overall: 100%</p> <p><i>HAM-D 17</i> Baseline n G1: 22 G2: 24 Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)</p> <p><i>BDI:</i> Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p><i>HAM-D 17</i> Analyzed n G1: 22 G2: 23</p> <p>Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 <i>P</i> = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR <i>P</i> = 0.93</p> <p>Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 <i>P</i> = 0.017</p> <p>Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p>Remitters, n HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22</p> <p>Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5)</p> <p>Other: QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</p> <p>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (<i>p</i> = 0.987). This</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>major depressive episodes in patients referred for ECT</p> <p><i>Quality Rating</i> Good</p>	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions: daily for 15 days <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 			<p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD) NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	<p>suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales (verbal fluency,</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>anterograde memory, and retrograde memory)</p> <p><i>MMSE</i> Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9) Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)</p> <p>Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3)</p> <p>Change, mean (SD): G1: 1.3 G2: -1.3 <i>P</i> < 0.08</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p> <p>Attrition Overall to end of treatment 6/46, at 6 months 9/46 At end of treatment, % G1: 6/24 G2: 0</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0 Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Paykel, 1999³⁸ Scott, 2000⁵⁹ Scott, 2003⁶⁰ Paykel, 2005⁶¹</p> <p>Note: #2223, #2219, #274, and #3815 are companion studies, data was abstracted in toform for #2219.</p> <p><i>Country, setting</i> UK, outpatient Retrospective analysis: Inpatient or Outpatient</p> <p><i>Funding</i> Medical Research Council, London, England and a grant from Oxford and Anglia Region</p> <p><i>Research Objective</i> To compare cognitive</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 158 Retrospective analysis: 135</p> <p><i>Duration</i> Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks. Retrospective analysis: wks 69 and onward (up to 6 years)</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, Residual symptoms had lasted 2 to 18 months. 	<p><i>Treatment Failure</i> Mean failed trials G1: NR G2: NR Retrospective analysis: G3: NR G4: NR</p> <p><i>Polarity, %</i> Unipolar 100% Retrospective analysis: G3: NR</p> <p><i>G4: NRAge, mean yrs</i> G1: 43.2 (11.2) G2: 43.5 (9.8) Retrospective analysis: G3: 48.6 G4: 49.8</p> <p><i>Sex, % females</i> G1: 53% G2: 46%</p>	<p><i>HAM-D 17</i> G1: Clinical Management only G2: CT plus Clinical Management</p> <p>Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2)</p> <p>Follow up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7)</p> <p>Follow up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3)</p> <p>Retrospective analysis: Mean scores at end of study G3: 7.3 (5.5) G4: 8.0 (6.4)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 20% did not adhere to protocol through to study end or relapse point Retrospective analysis: 14.5% Reasons for Overall Attrition: Deceased, n = 7; Refused, n = 11; Non-response to request, n = 3, Not traceable, n = 2</p> <p>At end of treatment, % G1: 4 G2: 14</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintenance treatment with antidepressants.</p> <p>Retrospective analysis: To restudy subjects approximately 6 years after randomization, or 4 1/2 years after completion of the trial and its follow-up phase</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Interventions</i> G1: Clinical management Only G2: CT plus Clinical Management Retrospective Analysis G3: Clinical management only G4: CT plus Clinical Management</p> <p><i>Medications allowed</i> Continued on current medications with dose adjustments allowed</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16</p>	<ul style="list-style-type: none"> • Failure required to be in the current episode • Retrospective Analysis Relapse defined as return to Major depression for 4 wks or, during the follow-up trial phase only, persistent residual symptoms for at least 8 weeks reaching 13 on the HAM-D in two successive rating 8 wks apart and producing a sufficient level of distress or dysfunction to mandate withdrawal from treatment constraints. <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Unipolar depression, aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression within last 18 months but not in last 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase 	<p>Retrospective analysis: G3: 52% G4: 50%</p> <p><i>HAM-D 17</i> Baseline n G1: 78 G2: 80</p> <p>Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)</p>	<p>Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 P = NS</p> <p>Follow up at 44 weeks G1: - 3.0 G2: -4.5</p> <p>Follow up at 68 weeks G1: -5.0 G2: -4.9</p> <p>Responders, n NR</p> <p>Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24)</p> <p>Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45)) Retrospective analysis: Remission by 68 weeks G3: 30 G4: 42</p> <p><i>BDI</i> Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6),</p>	<p>At end of followup, % G1: 12 G2: 10</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]</p>

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<p>inhibitor for at least previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose.</p> <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, • any other primary Axis I disorder at time of index illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT 		<p>Follow up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3)</p> <p>Follow up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7)</p> <p>Change, mean (SD) At week 20 G1: -6.24 G2: -8.44</p> <p>Responders, n NR</p> <p>Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%)</p> <p>Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36)</p> <p>Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT</p>	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		for more than 5 sessions.		<p>Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI (0.32, 0.93). Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219: Relapse was defined as: (1) meetingDSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms during follow up phase between 2 successive ratings 2 months apart, reaching</p>	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>a score onHAM-D 17 of at least 13 on both occasions and a level of distress or dysfunction for which the withholding of additional active treatment was no longer justified</p> <p>Retrospective Analysis Acutarial Kaplan-Meier recurrence rates (%): Wk 20 (from randomization): G1: 24 G2: 5 Difference (95% CI), p-value: 19 (8 to 30), p = 0.002 Wk 68 (from randomization): G1: 34 G2: 23 Difference (95% CI), p-value: 11 (-3 to 25), p = 0.07 Wk 120(from randomization): G1: 43 G2: 83 Difference (95% CI), p-value: 5 (-11 to 21), p = 0.25 Wk 172 (from randomization): G1: 49 G2: 41</p>	

Evidence Table 10. KQ 2 – Tier 2: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Difference (95% CI), p-value: 8 (-8 to 24), p = 0.16 Wk 224 (from randomization): G1: 55 G2: 56 Difference (95% CI), p-value: -1 (-17 to 15), p = 0.52 Wk 275 (from randomization): G1: 65 G2: 60 Difference (95% CI), p-value: 5 (-11 to 21), p = 0.33	

*This study came from an unpublished source (conference proceeding).

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Grunhaus et al., 2000⁶²</p> <p><i>Country, setting</i> Israel Sheba Medical Center, inpatients and outpatients</p> <p><i>Funding</i> Established Investigator Award of NARSTAD</p> <p><i>Research Objective</i> To compare rTMS to ECT and psychotic vs. non-psychotic</p> <p><i>Quality Rating</i> Poor</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 40</p> <p><i>Duration</i> Varied – ECT patients treated for average of 5 weeks, and rTMS pts treated for 4 weeks. Primary outcome measured at end of treatment</p> <p><i>Interventions</i> Overall G1: ECT G2: rTMS</p> <p>Pts with psychosis G3: ECT: G4: rTMS</p> <p>Pts without psychosis G5: ECT G6: rTMS</p> <p><i>Medications allowed</i> • ECT allowed benzodiazepines, neuroleptics antidepressants and anticonvulsants in stable doses</p>	<p><i>TRD definition</i> • Pts referred for ECT • Only some patients treatment resistant (not defined). Treatment failure not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • age over 18 • DSM-IV diagnosis of MDD • HAM-D17 ≥18 • no personal or first-degree relative history of seizure • no medical, neurological, or neurosurgical disorder that would preclude administration of ECT or rTMS.</p> <p><i>Exclusion criteria</i> • Additional Axis-1 diagnoses</p>	<p><i>Subgroups</i> Patients with and with out Psychosis</p> <p><i>Treatment Failure</i> Failed ≤1 trial, % G1: 50 G2: 25</p> <p>Failed ≥2 trials, % G1: 50 G2: 75</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 63.6 (15.0) G2: 58.4 (15.7)</p> <p><i>Sex, % females</i> G1: 70 G2: 60</p> <p><i>HAM-D 17</i> Baseline n Overall G1: 20 G2: 20</p> <p>Patients with Psychosis G3: 10 G4: 9</p> <p>Patients without Psychosis G5: 10 G6: 11</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) At week 2 G1: 17.6 (7.4) G2: 19.3 (8.6) G3: 15.5 (7.6) G4: 23.4 (5.5) G5: 19.7 (7.0) G6: 15.8 (9.3)</p> <p>End of treatment G1: 11.2 (8.4) G2: 15.4 (7.5) G3: 8.4 (5.3) G4: 20.8 (5.0) G5: 13.9 (10.3) G6: 11.0 (6.2)</p> <p>Change, mean (SD) At week 2 G1: 10.8 G2: 6.5 G3: 16.0 G4: 5.3 G5: 5.5 G6: 7.7</p> <p>End of treatment G1: 17.2 G2: 10.4 Group x time, <i>P</i> = 0.09 G3: 23.1 G4: 7.9 Group x time, <i>P</i> = 0.005 G5: 11.3 G6: 12.5 Group x time, <i>P</i> = NS</p>	<p><i>Quality of Life</i> Scale Pittsburg Sleep Quality Index</p> <p>Intervention G1: ECT G2: rTMs G3: G4: ECT Psychotic vs none G5: rTMS Psychotic vs none</p> <p>Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11</p> <p>Baseline score, mean (SD) G1: 12.5 (4.4) G2: 11.7 (5.7) G3: G4: 12.1 (5.5) vs 12.9 (3.1) G5: 14.1 (4.9) vs 9.7 (5.8)</p> <p>Endpoint score, mean (SD) G1: Awk2 8.8 (4.5)/endpoint 6.8 (3.5)</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>• rTMS All psychiatric medications were discontinued only clonazepam (1–2 mg/day, given in twice-daily doses) was started in all patients to decrease anxiety, provide relief of severe insomnia, and have an additional protective element regarding seizures</p> <p><i>Strategy</i> Mixed-between group differences</p> <p><i>Parameters</i> ECT: • % receiving bilateral: 40 switched after non-response • Intensity 2.5-fold seizure threshold • Number of sessions - mean 9.6 sessions (range 7-14)</p> <p>rTMS Low • Frequency (Hz): • Motor threshold (%): • Number of trains: • Length of train (seconds): • Inter-train interval:</p>		<p>Baseline score, mean (SD) G1: 28.4 (9.3) G2: 25.8 (6.1) G3: 31.5 (11.5) G4: 28.7 (5.6) G5: 25.2 (5.3) G6: 23.5 (5.6)</p>	<p>Responders if the final HRSD had decreased to 50% or more from baseline and the final GAS < 60.</p> <p>Responders, n End of txt G1: 16 (80%) G2: 9 (45%) <i>P</i> < 0.05 G3: 10 (100%) G4: 2 (22%) <i>P</i> ≤ 0.01 G5: 6 (60%) G6: 7 (63%) <i>P</i> = NS</p>	<p>G2: Awk2 10.1 (3.7)/endpoint 10.5 (3.9) G3: G4: Awk2 8.0 (4.5)/endpoint 5.8 (2.1) vs Awk2 8.0 (4.5)/endpoint 5.8 (2.1) G5: Awk2 12.2 (2.8)/endpoint 12.3 (3.6) vs. Awk2 8.4 (3.5)/endpoint 9.1 (3.8)</p> <p>Change, mean (SD) G1: Awk2 3.7/endpoint 5.7 G2: Awk2 1.6/endpoint 1.2 G3: G4: Awk2 4.1/endpoint 6.3 vs Awk2 4.9/endpoint 7.1 G5: Awk2 11.9/endpoint 1.8 vs. Awk2 1.3/endpoint 0.6</p> <p>Other Overall Group F 1.8 (df 1,36) <i>P</i> = NS Time F 12.5 (df 2,72) <i>P</i> = 0.000</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Pulses per session: • Total number of sessions: <p>rTMS High</p> <ul style="list-style-type: none"> • Frequency (Hz): • Motor threshold (%): • Number of trains: • Length of train (seconds): • Inter-train interval: • Pulses per session: • Total number of sessions: 				<p>Interaction F 4.6 (df 2,2) P = 0.010</p> <p>Non-psychotic Group F 0.5 (df 1,18) P = NS</p> <p>Time F 4.4 (df 2,36) P = 0.020</p> <p>Interaction F 2.3 (df 2,2) P = NS</p> <p>Psychotic Group F 9.8 (df 1,16) P = 0.006</p> <p><i>Quality of Life</i> Overall Group F 1.8 (df 1,36) P = NS</p> <p>Time F 12.5 (df 2,72) P = 0.000</p> <p>Interaction F 4.6 (df 2,2) P = 0.010</p> <p>Non-psychotic Group F 0.5 (df 1,18) P = NS</p> <p>Time F 4.4 (df 2,36) P = 0.020</p> <p>Interaction F 2.3 (df 2,2) P = NS</p> <p>Psychotic Group F 9.8 (df 1,16) P = 0.006</p> <p>Scale Global Assessment of Function Scale</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Intervention G1: ECT G2: rTMS G3: G4: ECT Psychotic vs none G5: rTMS Psychotic vs none</p> <p>Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11</p> <p>Baseline score, mean (SD) G1: 31.0 (8.5) G2: 34.1 (11.7) G3: Intervention4: 29.0 (7.0) vs. 33.0 (9.8) G5: 28.9 (9.9) vs. 38.3 (11.8)</p> <p>Endpoint score, mean (SD) G1: Awk2 46.8 (17.2)/ endpoint 61.5 (21.5) G2: Awk2 44.5 (14.7)/ endpoint 51.0 (18.2) G3: G4: Awk2 50.6 (18.3)/ endpoint 65.5 (18.8) vs. Awk2 43.0 (16.0)/ endpoint 57.5 (24.2)</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>G5: Awk2 36.1 (8.2)/ endpoint 39.4 (14.5.) vs. Awk2 51.4 (15.5)/ endpoint 60.5</p> <p>Change, mean (SD)</p> <p>G1: Awk2 15.8/endpoint 30.5</p> <p>G2: Awk2 10.4/endpoint 16.9</p> <p>G3:</p> <p>G4: Awk2 21.6/endpoint 36.5 vs. Awk2 10.0/endpoint 24.5</p> <p>G5: Awk2 7.2/endpoint 10.5 vs. Awk2 13.1/endpoint 22.2</p> <p>Other</p> <p>Overall</p> <p>Group F 0.7 (df 1,38) <i>P</i> = NS</p> <p>Time F 40.8 (df 2,76) <i>P</i> = 0.000</p> <p>Interaction F 3.4 (df 2,2) <i>P</i> = 0.040</p> <p>Non-psychotic</p> <p>Group F 1.0 (df 1,19) <i>P</i> = NS</p> <p>Time F 19.8 (df 2,38) <i>P</i> = 0.000</p> <p>Interaction F 0.3 (df 2,2) <i>P</i> = NS</p> <p>Psychotic</p> <p>Group F 8.2 (df 1,17) <i>P</i> = 0.01</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Adverse Events</i> NR 5 rTMS patients had mild headaches</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Measures, Results MMS. (ECT baseline 25.9 (4.1), ECT end of treatment 24.5 (7.6); rTMS baseline 24.8 (4.1), rTMS end of treatment 26.3 (3.9), repeated measures ANOVA [group effect $F(1,29) = 0.1, P = NS$; time effect $F(2,58) = 1.3, P = NS$; interaction $F(2,2) = 2.3, P = NS$) analysis was also performed for psychotic–nonpsychotic groups with similar results.</p> <p>Predefined No</p> <p><i>MMSE</i></p> <p>Baseline n G1: 20 G2: 20</p> <p>Baseline score, mean (SD) G1: 25.9 (4.1) G2: 24.8 (4.1)</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Endpoint score, mean (SD) G1: 24.5 (7.6) G2: 26.3 (3.9)</p> <p>Change, mean (SD) G1: -1.4 G2: +1.5</p> <p>Other ANOVA [group effect F(1,29) = 0.1, P = NS; time effect F(2,58) = 1.3, P = NS; interaction F(2,2) = 2.3, P = NS) analysis was also performed for psychotic–nonpsychotic groups with similar results.</p> <p>Adequate information</p> <p><i>Attrition</i> Overall, % 0%</p> <p>At end of treatment, % 0</p> <p>At end of followup, % 0</p> <p>Withdrawals due to efficacy, % 0</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> Compliance All patients completed study
<p><i>Author, Year</i> Dannon, 2002⁴⁵</p> <p><i>Country, setting</i> Israel; medical center outpatient program</p> <p><i>Funding</i> National Association for Research in Schizophrenia and Affective Disorders (NARSAD) and Stanley Research Foundation</p> <p><i>Research Objective</i> To compare longitudinal outcomes of patients who responded to either rTMS or ECT</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Study references Grunhaus 2000 (Refid #368) which is open study of 40 patients - suspect this is continuation of this with additional patients. Of 43 responders initially identified, 2 are excluded</p> <p><i>N</i> 43</p> <p><i>Duration</i> 3 month and 6 month follow-up; Primary outcome was presence or absence of relapse at 3 or 6 months. Relapse defined as return of depressive symptomatology meeting DSM-IV criteria</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • Not required or not specified to be in current episode <p><i>Setting(s)</i> Outpatient</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Responded to treatment with either ECT or rTMS • over age 18 years • DSM-IV diagnosis of MDD with or without psychotic features • no personal or first-degree family history of seizure • no major medical, neurologic, or neurosurgical disorder. <ul style="list-style-type: none"> • Response for inclusion defined as HAM-D17 <= 10 or demonstrating 60% drop in HAM-D and final global 	<p><i>Subgroups</i> No sub-group analysis of psychosis although permitted in study</p> <p><i>Treatment Failure</i> Patients referred for ECT because of nonresponse or psychotic MDD</p> <p>Failed 1 or more, % G1: NR G2: NR</p> <p>Failed 2 or more, % G1: NR G2: NR</p> <p>Current episode failures, mean G1: NR G2: NR</p> <p>Mean failed trials G1: NR G2: NR</p>	<p><i>HAM-D 17</i></p> <p>Baseline n G1: 20 G2: 21</p> <p>Baseline score, mean (SD) G1: 7.90 (4.54) G2: 7.75 (3.74)</p> <p>Endpoint score, mean (SD) At 3 months G1: 7.71 (5.03) G2: 6.40 (4.91) At 6 months G1: 8.40 (5.60) G2: 7.90 (7.14)</p> <p>Change, mean (SD) At 3 months G1: -0.01 G2: 1.35 At 6 months G1: -0.5 G2: -0.15</p>	<p><i>Quality of Life</i> Global Assessment of Functioning (GAF), or GAS</p> <p>Baseline n G1: 20 G2: 21</p> <p>Baseline score, mean (SD) G1: 71.81 (10.39) G2: 72.50 (9.39)</p> <p>Endpoint score, mean (SD) At 3 months G1: 75.52 (13.81) G2: 79.75 (12.92) At 6 months G1: 72.8 (11.94) G2: 77.75 (17.13)</p> <p>Change, mean (SD) At 3 months G1: -3.71 G2: -7.25</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>for MDD with a HAM-D17 score of ≥ 16 points</p> <p><i>Interventions</i> A - Electroconvulsive Therapy (ECT) B - Repetitive Transcranial Magnetic Stimulation (rTMS) G1: ECT G2: rTMS Antidepressants prescribed at end of ECT and rTMS for all patients</p> <p><i>Parameters</i> rTMS: Location = Left Dorsolateral Prefrontal Cortex Frequency = 10Hz Intensity = 90% MT Per Session = 6 sec trains with 30 sec interval in between at 20 times. Number of sessions = daily for 20 days ECT Methods: Location: Initially unilateral; switched to bilateral txt after 6th txt if HRSD had not decreased by $\geq 30\%$ Threshold = 2.5 times threshold energy to maintain a seizure</p>	<p>assessment scale (GAS) ≥ 60</p> <p><i>Exclusion criteria</i> NR in this article - but Grunhaus 2000 (Refid #368) reports that patients with additional axis-I diagnoses were excluded from the study</p>	<p>Previous treatment, not specified, % G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: NR G2: NR</p> <p>Bipolar I G1: NR G2: NR</p> <p>Bipolar II G1: NR G2: NR</p> <p><i>Age, mean yrs</i> G1: 57.43 G2: 56.85</p> <p><i>Sex, % females</i> G1: 70% G2: 66.7%</p> <p>Note: there might be a typo in table in reporting gender ratio, percentage reported here is based on numbers in "rTMS" column in paper because they add up to correct n for "ECT column."</p>	<p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Relapse (HAM-D ≥ 16) At 3 months G1: 2 G2: 1 At 6 months G1: 2 G2: 3 Combined G1: 4 G2: 4</p> <p>Other HAM-D17 3 mos = $P = NS$, CI -1.83, 4.46; 6 mos = $P = NS$, CI -3.61, 4.61 ECT vs. rTMS</p> <p><i>BDI</i> NR</p> <p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> No</p>	<p>At 6 months G1: -0.99 G2: -5.25</p> <p>Other 3 mos $P = NS$, CI -12.69, 4.23; 6 mos $P = NS$, CI -14.40, 4.50</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined NA - No AE data reported</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 4.6%</p> <p>At end of treatment, % NR</p> <p>At end of followup, % G1: 0 G2: 9</p>

Evidence Table 11. KQ 3 – Tier 3: Maintaining remission or treating patients with unresponsive or recurrent disease (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>length of >= 25 sec. Number of sessions = NR</p> <p><i>Strategy</i> There is no description of whether participants were taking medications prior to treatment with ECT or rTMS. Co-mediations were not allowed during period when ECT or rTMS was given with exception of lorazepam. Antidepressants</p>		<p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR</p> <p>Groups similar at baseline No- what are differences All P values were reported as non-significant for baseline characteristics, however following characteristics showed some variation between groups: Duration of episode (months) (mean +/- SD), ECT group = 6.71 +/- 7.56, rTMS group</p> <p><i>Tier</i> Tier 3 only mention of whether participants failed any previous treatments is in Grunhaus (#368).</p>	<p>NR</p> <p>Baseline n NR</p> <p>Endpoint score, mean (SD) NR</p> <p>Achieving 1 or 2 score, % (SD) NR</p> <p>Other NR</p> <p><i>Other</i></p>	<p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: NR G2: NR</p> <p>Other</p> <ul style="list-style-type: none"> • 43 people agreed to be part of study, two were dropped before final analysis, no explanation is given, and they are not included in final analysis. • The Michigan Adequacy of Treatments (MATS) was also included in this study. MATS for ECT was 3 mos FU 1.92 (1.04 SD), 6 mos FU 1.82 (0.98 SD); rTMS 3 mos FU 2.28 (1.07 SD), 6mos 2.44 (1.03 SD). CI for 3 mos FU ECT vs. rTMS is -1.14 - 0.43, P = N <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Rosa et al, 2006²</p> <p><i>Country, setting</i> Brazil, university clinic, inpatients and outpatients included</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Included completers analysis & ITT (LOCF), ITT is reported in abstraction</p> <p><i>N</i> 42</p> <p><i>Duration</i> Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medications allowed</i> ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed</p> <p><i>Strategy</i> Switch</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) Not required or not specified to be in current episode <p><i>Tier 1 Inclusion criteria</i></p> <ul style="list-style-type: none"> Age 18-65 unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease Use of cardiac pacemaker Pregnancy 	<p><i>Treatment Failure</i></p> <p>Previous treatment, not specified, % Overall:100%</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 46.0 G2: 41.8</p> <p><i>Sex, % females</i> G1: 46.7 G2: 60.0</p> <p><i>Race, % white</i> G1: 80.0 G2: 90.0</p> <p><i>HAM-D 17</i> Baseline n G1: 20 G2: 22</p> <p>Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20]</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) NR (graph only)</p> <p>Change, mean (SD) NR (graph only) P = 0.86</p> <p>Responders, n (%) G1: 6 (20) G2: 10 (45) P = 0.35</p> <p>Remitters, n (%) Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) P = 0.65</p> <p>Instrument CGI Endpoint score, mean (SD)</p> <p>2wk G1: 4.0 (1.0) G2: 3.7 (1.1)</p> <p>4wk G1: 3.2 (1.5) G2: 3.1 (1.3)</p> <p>Change, mean (SD) NR, P = 0.672</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Suicidality, % G1: 10.0 G2: 9.1</p> <p>rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study</p> <p><i>Neuropsychological or executive functioning</i> NS differences between groups on all neuropsychological tests following wk2 & wk4. (Weschler Adult Intelligence Scale - R subtests (Vocabulary, Cube)</p> <p>Wechsler Memory Scale subtest (Digit Span)</p> <p>Rivermead Behavioral Memory Test)</p>

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> rTMS:</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5) 		<p><i>CGI</i> Baseline n G1: 20 (N analyzed =15) G2: 22 (N analyzed =20)</p> <p>Baseline score, mean (SD) G1: 4.7 (0.8) G2: 4.3 (0.8)</p>		<p><i>MMSE</i> NR</p> <p><i>Other</i></p> <p><i>Attrition</i> Overall, % 16.7</p> <p>At end of treatment, % G1: 15.0* G2: 9.1* *Prior to completing txt (txt end date differed by pt)</p> <p>At end of follow-up, % G1: 25.0 G2: 9.1</p> <p>Withdrawals due to efficacy, % G1: NR G2: 0.0</p> <p>Withdrawals due to adverse events, % G1: NR G2: 9.1</p> <p>Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy <i>Adherence/ compliance</i> NR</p>

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Schulze-Rauschenbach et al., 2005⁶³</p> <p><i>Country, setting</i> Germany, Psychiatric University Hospital, inpatients</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> To compare neurocognitive effects of unilateral ECT and rTMS using a control</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Observational study of patients completing txt</p> <p><i>N</i> 30</p> <p><i>Duration</i> Not clear- testing took place 8.8 days on average after last treatment. Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks.</p> <p><i>Interventions</i> Control G1: ECT G2: rTMS</p> <p><i>Medications Allowed</i> Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study</p> <p><i>Parameters</i> ECT:</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks Not required or not specified to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Consecutively admitted patients with DSM-IV diagnosis of MDD Age over 18 years <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Previous treatment with ECT or rTMS Additional Axis I diagnosis 	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 46.7 G2: 47.7</p> <p><i>Sex, % females</i> G1: 50 G2: 44</p> <p><i>HAM-D 17</i> Baseline n G1: 14 G2: 16</p> <p>Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5)</p> <p><i>BDI</i> Baseline n G1: 14 G2: 16</p> <p><i>SSMQ</i> Baseline n G1: 14 G2: 16</p> <p>Baseline score, mean (SD)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9)</p> <p>Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, <i>P</i> = NS</p> <p>Responders, n G1: 6 (46%) G2: 7 (44%) <i>P</i> = 0.90</p> <p><i>BDI</i> Change, mean (SD) G1: 7.6 G2: 6.4 Group x time, <i>P</i> = NS</p> <p><i>SSMQ</i> Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8)</p> <p>Change, mean (SD) G1: 5.5 G2: 20.6</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included.</p> <p><i>Neuropsychological or executive functioning</i> Test scores</p> <ul style="list-style-type: none"> ECT Pre / Post vs. rTMS Pre / Post Post; <i>P</i> = Post Ect vs. Post rTMS Learning and anterograde memory <p>AVLT</p> <ul style="list-style-type: none"> Immediate recall (trials 1-5); <i>P</i> = NS Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); <i>P</i> < 0.01 Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); <i>P</i> < 0.05 Recognition hits; <i>P</i> = NS and Recognition

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) <p>rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: 400-600 • Total number of sessions: 2-3/wk <p><i>Strategy</i> Augment or add-on</p>		<p>G1: -20.7 (19.0) G2: -16.8 (16.9)</p>		<p>false alarms; $P = NS$</p> <p>MPT</p> <ul style="list-style-type: none"> • Recall; $P = NS$ and Delayed recall; $P = NS$ <p>Retrograde memory</p> <p>Retrograde AVLT</p> <ul style="list-style-type: none"> • Recall; $P = NS$ and Recognition hits; $P = NS$ • Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); $P < 0.05$ <p>Four-card task</p> <ul style="list-style-type: none"> • Free recall 0.4 (0.5) vs. 1.4 / (1.2); $P < 0.05$ • Recognition; $P = NS$ • AMI Recall score; $P = NS$ <p>Subjective memory</p> <ul style="list-style-type: none"> • SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); $P < 0.05$ <p>Other cognitive functions</p> <ul style="list-style-type: none"> • MMSE; $P = NS$, TrailMakingTest A; $P = NS$, TrailMakingTest B; $P = NS$, Digit span (WAIS-R); $P = NS$, Letter-number span;

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>P</i> = NS, Word fluency (LPS); <i>P</i> = NS</p> <p><i>MMSE</i> G1: ECT G2: rTMS G3: Control</p> <p>Baseline n G1: 14 G2: 16 G3: 15</p> <p>Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0)</p> <p>Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1)</p> <p>Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01</p> <p>Other <i>P</i> = NS</p> <p><i>Attrition</i> Overall, % 3.3 At end of treatment, % G1: 7</p>

Evidence Table 12. KQ 4. Cognitive Functioning: Tier 1 (ECT vs. rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>G2: 0</p> <p>At end of follow-up, % G1: NR G2: NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 0</p> <p>Withdrawals due to adverse events, % G1: 7 G2: 0</p> <p>One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included in analysis</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰</p> <p><i>Country, setting</i> USA, Single center, University department of psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good</p> <p>Fair for KQ2 and subgroups¹¹ (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint</p> <p><i>Interventions</i> G1: High-left TMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazepines G1: 26% vs. G2: 24</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥ 3 on ATHF) • Failures not required to be in current episode</p> <p><i>Tier 1 Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous TMS exposure • Bipolar disorder • Previous failure of nine or more bitemporal ECT treatments • Current major depressive episode longer than 5 years • History of substance abuse or dependence within past 2 years, • Antisocial or borderline personality disorder,</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p><i>Baseline n</i> G1: 35 G2: 33</p> <p><i>Treatment Failure</i> Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67)</p> <p>Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 44.3 G2: 44.2</p> <p><i>Sex, % females</i> G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 15.7 G2: 19.8</p> <p>Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time $P = 0.002$</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) $P = 0.008$</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) $P = 0.033$</p> <p>No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse)</p> <p><i>BDI</i> Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed significant group by time interaction ($P = 0.003$)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33).</p> <p>The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 ($t = 4.24, P < 0.001$).</p> <p>Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms. (Data = NR)</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Those stopping medications had to be medication-free for at least 2 weeks All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> Frequency (Hz):10 Motor threshold (%): 110 Number of trains: 32 Length of train (seconds): 5 Inter-train interval: 25-30 Pulses per session: 1600 Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> Identical stimulation parameters Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> Active suicidal ideation Vurrent symptoms of psychosis, Hx of seizure disorder, Hx of closed head injury with loss of consciousness or prior brain surgery Any other major psychiatric or medical comorbidity 	<p>Groups similar at baseline Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>		<p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$)</p> <p>no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures., There was significant improvement in individual neuropsychological test performances for both groups.</p> <p>No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session.</p> <p><i>MMSE</i> NR</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Holtzheimer et al., 2004¹⁹</p> <p><i>Country, setting</i> USA, single center, outpatient/inpatient status not clearly stated</p> <p><i>Funding</i> University of Washington</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 15</p> <p><i>Duration</i> Primary endpoint following 2 weeks of treatment and follow-up 1 week after txt</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Subjects must have failed at least 2 previous antidepressant trials due to lack of response to adequate trial (defined by ATHF) or medication intolerance Not required or not specified to be in current episode 	<p><i>Treatment Failure</i></p> <p>Failed 7 or more, % G1: 85.7 G2: 37.5</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 40.4 G2: 45.4</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD)</p> <p>At week 1 G1: 18.0 (1.2) G2: 18.0 (2.7)</p> <p>At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i> Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable</p> <p><i>Quality Rating</i> Fair</p>	<p>completed</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> All pts discontinued (failed) AD medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 30-60 • Pulses per session: 1600 • Total number of sessions: 10 over 2 wks <p>Sham rTMS</p> <ul style="list-style-type: none"> • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp 	<p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 \geq 18 <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy 	<p><i>Sex, % females</i> G1: 57.1 G2: 42.9</p> <p><i>Right handed, %</i> G1: 100 G2: 100</p> <p><i>HAM-D 17</i> Baseline n G1: 7 G2: 8</p> <p>Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)</p>	<p>1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1)</p> <p>Change, mean (SD) At week 1 G1: 4.7 G2: 2.8</p> <p>At week 2 G1: 8.1 G2: 5.5</p> <p>1 week follow-up G1: 3.9 G2: 3.2 All endpoints, <i>P</i> = NS</p> <p>Responders, n (%) At week 1 G1: 0 G2: 0</p> <p>At week 2 G1: 2 (28.6) G2: 1 (12.5)</p> <p>1 week follow-up G1: 0 G2: 0</p> <p><i>BDI</i> Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)</p>	<p><i>Neuropsychological or executive functioning</i> Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); <i>P</i> < 0.05).</p> <p>No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.</p> <p><i>MMSE</i> NR There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4)</p> <p>1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9)</p> <p>Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1</p> <p>Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), P = NS</p>	<p><i>Attrition</i> Overall, % 0 during treatment. 3 (20%) before final assessment at week 3</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % G1: 28.6 G2: 12.5</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p> <p><i>Adherence/ compliance</i> Compliance All 15 subjects completed all 10 txt sessions</p>
<p><i>Author, Year</i> Padberg et al., 1999²¹</p> <p><i>Country, setting</i> Germany, university clinic, patient status not clear</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 18</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • 2+ failed txt trials of 4+ wks duration including at least 1 tricyclic • Required to be in current episode 	<p><i>Treatment Failure</i></p> <p>Current episode failures, mean</p> <p>G1: 4.0 (2.2) G2: 3.2 (0.8) G3: 3.2 (1.2)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD)</p> <p>G1: 28.5 (9.4) G2: 21.5 (21.5) G3: 23.5 (10.4)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i></p> <p>Headache, % G1: 16.7 G2: 16.7 G3: NR</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Funding</i> Magstim Company Ltd. & Micromed Medizin-Elektronik GmbH</p> <p><i>Research Objective</i> Compare antidepressant efficacy and tolerability of fast, slow, and sham rTMS in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Duration</i> 1 week of active txt</p> <p>Primary outcome: Change in HAM-D after 5 txt sessions</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: Fast rTMS G2: SlowrTMS G3: Sham rTMS</p> <p><i>Medication allowed</i> 83.3% of pts continued on their current [failed] AD medication, others were not on a med and did not start one prior to trial</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS High • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 5 • Length of train (seconds): 5 • Inter-train interval: 30 • Pulses per session: 250</p>	<p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> MDD (DSM IV)</p> <p><i>Exclusion criteria</i> Organic brain disorders, contraindications for rTMS</p>	<p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 63.5 G2: 46.7 G3: 43.3</p> <p><i>Sex, % females</i> G1: 33.3 G2: 83.3 G3: 66.7</p> <p><i>Right handed, %</i> G1: 100 G2: 100 G3: 100</p> <p><i>HAM-D 21</i> Baseline n G1: 6 G2: 6 G3: 6</p> <p>Baseline score, mean (SD) G1: 30.2 (9.5) G2: 26.7 (9.4) G3: 22.2 (8.8)</p> <p><i>MADRS</i> Baseline n G1: 6 G2: 6 G3: 6</p>	<p>Change, mean (SD) G1: -1.7 G2: -5.2 G3: -1.3 <i>P</i> > 0.05</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p><i>MADRS</i> Endpoint score, mean (SD) graph only</p> <p>Group x time, <i>P</i> < 0.1</p>	<p>Focal Pain at rTMS site during stimulations, %: G1: 50 G2: 33.3 G3: 0</p> <p>There were no serious AE.</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Verbal Memory Tests (included 3 learning trials and a consecutive, delayed recall task after distraction):</p> <p>Verbal memory performance improved significantly after fast rTMS</p> <p>Learning 1. <i>P</i> = 0.006 2. NA 3. Fast rTMS improvement <i>P</i> = 0.032, Slow rTMS <i>P</i> = NS, Sham decrease in performance <i>P</i> = 0.09</p> <p><i>MMSE</i> NR</p>

Evidence Table 13. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Total number of sessions: 5/wk <p>rTMS Low</p> <ul style="list-style-type: none"> • Frequency (Hz):0.3 • Motor threshold (%): 90 • Number of trains: 10 • Length of train (seconds): 25 • Inter-train interval: NR • Pulses per session: 75 • Total number of sessions: 5/wk <p>Sham:</p> <ul style="list-style-type: none"> • Same as high rTMS except coil angled at 90 degrees with 1 wing resting on skull 		Baseline score, mean (SD) graph only		<p><i>Attrition</i></p> <p>Overall, % NR, "no pts asked for discontinuation of rTMS"</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> NR - "compliance was excellent"</p>

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Fitzgerald et al., 2003¹⁵</p> <p><i>Country, setting</i> Australia 2 general psychiatric services, outpatients</p> <p><i>Funding</i> National Health and Medical Research Council and a grant from Stanley Medical Research Institute</p> <p><i>Research Objective</i> To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 60</p> <p><i>Tier 1</i></p> <p><i>Duration</i> Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt.</p> <p><i>Interventions</i> G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham</p> <p><i>Medications Allowed</i> 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics</p>	<p><i>TRD definition</i> • Failed a minimum of 2 courses of antidepressant medications (6+ weeks)</p> <p>Not required or not specified to be in current episode</p> <p><i>Inclusion criteria</i> • DSM-IV diagnosis of Major Depression (included bipolar depression)</p> <p><i>Exclusion criteria</i> • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders</p>	<p><i>Treatment Failure</i> Mean failed trials Overall (SD) 5.68 (3.40) Polarity, %</p> <p>Bipolar I G1: 5 G2: 5 G3: 20</p> <p><i>Age, mean yrs</i> G1: 42.2 G2: 45.55 G3: 49.15</p> <p><i>Sex, % females</i> G1: 40 G2: 35 G3: 55</p> <p><i>Right handed, %</i> G1: 90 G2: 100 G3: 85</p> <p><i>BDI</i> Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)</p>	<p><i>BDI</i> Endpoint score, mean (SD)</p> <p>At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7)</p> <p>Change, mean (SD) At 2 weeks G1:- 6.4 G2: -7.8 G3: -2.3 P = 0.03</p> <p><i>MADRS</i> Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5)</p> <p>Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) P = 0.004 G1: vs. G3, G2 vs. G3, P < 0.005 Responders, n 20% ≤ decrease</p>	<p><i>Quality of Life</i> GAF Global Assessment of Functioning</p> <p>Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)</p> <p>Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8)</p> <p>Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5 Overall group F56,2=2.6; P =.08; LFR-TMS vs sham: P = 0.03; and HFLTMS vs sham: P = 0.09</p> <p><i>Quality of Life</i> Overall group</p>

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS LowFrequency (Hz):1</p> <ul style="list-style-type: none"> • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week <p>rTMS High</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week <p>Sham rTMS</p> <ul style="list-style-type: none"> • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week 		<p><i>MADRS</i> Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)</p>	<p>At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) <i>P</i> = 0.07</p> <p>Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 <i>P</i> = NR</p> <p><i>CGI</i> Endpoint score, mean (SD) NR <i>P</i> =.01</p>	<p>F56,2=2.6; <i>P</i> =.08; LFR-TMS vs sham: <i>P</i> = 0.03; and HFLTMS vs sham: <i>P</i> = 0.09</p> <p><i>Adverse Events</i></p> <p>Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS.</p> <ul style="list-style-type: none"> • Although there was no difference in incidence of these adverse effects (<i>P</i> =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<ul style="list-style-type: none"> • Two patients (1 in each group) reported transient dizziness for a short time after treatment. <p>2wks - 4 wks:</p> <ul style="list-style-type: none"> • One patient withdrew after 1 session of HFL-TMS treatment in single-blind phase of study owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium <p><i>Neuropsychological or executive functioning</i></p> <ul style="list-style-type: none"> • No deterioration in performance was found in any cognitive • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on verbal paired associates (t50=-7.3;

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>$P < 0.001$), verbal fluency ($t_{48} = -3.8$; $P < 0.001$), and digit span forwards ($t_{48} = -1.8$; $P = 0.003$) subscales; Personal Semantic Memory Schedule ($t_{50} = -2.4$; $P = 0.02$); and Autobiographical Memory Schedule ($t_{50} = -1.9$; $P = 0.05$).</p> <ul style="list-style-type: none"> • A similar pattern of improvements was seen for each of • treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across sametimes. <p>MMSE NR</p> <p>Other</p> <p>Attrition Overall, % None in initial 2 week treatment phase</p>

Evidence Table 14. KQ 4. Cognitive Functioning: Tier 1 (rTMS vs sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>At end of treatment, % 0</p> <p>At end of follow-up, % NR But at least 28.3% did not continue on through 2nd 2 weeks</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Manes et al., 2001²⁹</p> <p>Includes additional neuro-psychological outcomes reported in Moser et al., 2002³⁰</p> <p><i>Country, setting</i> US, outpatient clinic</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To examine antidepressant efficacy of rTMS in a TRD population</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> cannot tell if ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> 2 weeks (1 week of treatment, 1 wk follow-up following last treatment)</p> <p>Primary outcomes HAM-D at end of treatment and at 1 week follow-up</p> <p><i>Interventions</i> G1: rTMS (N=10) G2: Sham rTMS (N=10)</p> <p><i>Medications allowed</i> No antidepressant medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20</p>	<p><i>TRD definition</i> • Not required or not specified to be in current episode</p> <p><i>Setting(s)</i> Outpatient Psychiatric</p> <p><i>Inclusion criteria</i> • Major/Minor Depression (DSM IV), • TRD (1+ failed trial)</p> <p><i>Exclusion criteria</i> NR</p>	<p><i>Subgroups</i> Age 50+</p> <p><i>Treatment Failure</i> Mean failed trials G1: 4 (2.3) G2: 4 (1.2)</p> <p><i>Polarity, %</i> Major Depression G1: 80 G2: 100 Dysthymia G1: 20 G2: 0</p> <p><i>Age, mean yrs</i> G1: 60.5 G2: 60.9</p> <p><i>Sex, % females</i> G1: 50 G2: 50</p> <p><i>Race, % white</i> G1: 100 G2: 100</p> <p><i>HAM-D</i> Baseline n G1: 10 G2: 10</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) At 1 week G1: 13.7 (5.4) G2: 16.2 (8.5)</p> <p>1 week Follow-up G1: 14.4 (6.4) G2: 15.5 (9.1)</p> <p>Change, mean (SD) At week 1 G1: -9 G2: -6.5</p> <p>1 week follow-up G1: -8.3 G2: -7.2 All time points <i>P</i> >0.66; pts with MDD only - <i>P</i> = 0.3919</p> <p>Responders, n (%) G1: 3 (30) G2: 3 (30) <i>P</i> = NS</p> <p>Remitters, n G1: 2 G2: 2 <i>P</i> = NR</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 40% G2: 0%</p> <p>Other: Local pain/local discomfort: 10%/40% vs. 0%/40%; anxiety: 0 vs 10%</p> <p><i>Neuropsychological or executive functioning</i> **30 (endpoint: mean of 3 days after 5 days of txt)</p> <p>Trail Making Test B score Baseline: rTMS: 87.22 Sham: 103.67 Follow-up rTMS: 58.59 Sham: 100.64 **some variation in pts included in two samples but reported as same study by authors. #1564 includes at least 1 participant <50 years old, n=19</p>

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk <p>Sham:</p> <ul style="list-style-type: none"> • Same stimulation, figure 8 coil was above top of skull and handle was placed against head 		<p>Baseline score, mean (SD)</p> <p>G1: 22.7 (5.2)</p> <p>G2: 22.7 (7.1)</p>		<p>Other neuropsychological tests showing no statistical significance in either group: Trail Making Test-A, Stroop Test, WAIS-R digit symbol, Controlled Oral Word Association, Boston naming test, stentance repetition, Rey Auditory Verbal Learning test, & Judgement of Line Orientation</p> <p><i>MMSE</i></p> <p>Baseline n</p> <p>G1: 10</p> <p>G2: 10</p> <p>Baseline score, mean (SD)</p> <p>G1: 28.7 (1.4)</p> <p>G2: 28.6 (1.3)</p> <p>Endpoint score, mean (SD)</p> <p>At Week 1</p> <p>G1: 29.6(0.7)</p> <p>G2: 29.3 (0.7)</p> <p>At Follow-up Week 1</p> <p>G1: 29.6(1.8)</p> <p>G2: 29.2 (0.8)</p> <p>Change, mean (SD)</p> <p>NR</p>

Evidence Table 15. KQ 4. Cognitive Functioning: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					1. $P > 0.41$ 2. $P = NA$ 3. $P = NR$ <i>Attrition</i> NR <i>Adherence/ compliance</i> NR

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> McLoughlin et al., 20077 Eranti et al., 2007⁸ Knapp et al., 2008⁹</p> <p><i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital in Invicta Mental Health Trust in Kent, 65.2% were inpatients</p> <p><i>Funding</i> National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating major depressive</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters)</p> <p><i>Type of analysis</i> m-ITT</p> <p><i>N</i> 46</p> <p><i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p>	<p><i>TRD definition</i> • All patients referred for ECT: • No failure required <i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Right handed patients • more than 18 years old • referred for ECT due to major depressive episode</p> <p><i>Exclusion criteria</i> • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.</p>	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0)</p> <p><i>Polarity, % MDD</i> G1: 91.67 G2: 90.91</p> <p><i>Bipolar</i> G1: 8.33% G2: 9.09 %</p> <p><i>Age, mean yrs</i> G1: 63.6 G2: 68.3</p> <p><i>Sex, % females</i> G1: 67.7 G2: 72.7</p> <p><i>Right handed, % Overall: 100%</i></p> <p><i>HAM-D 17 Baseline n</i> G1: 22 G2: 24</p> <p><i>Baseline score, mean (SD)</i> G1: 24.8 (5.0) G2: 23.9 (7.0)</p>	<p><i>HAM-D 17 Analyzed n</i> G1: 22 G2: 23</p> <p><i>Endpoint score, mean (SD)</i> End of treatment G1: 10.7 G2: 18.5 <i>P = 0.002, effect size of 1.44</i></p> <p><i>Follow-up at 6 months</i> G1: NR G2: NR <i>P = 0.93</i></p> <p><i>Change, mean (SD)</i> End of treatment G1: -14.1 G2: -5.4 <i>P = 0.017</i></p> <p><i>Responders, n</i> End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P = 0.005</i></p> <p><i>Remitters, n</i> HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P = 0.005</i></p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22</p> <p><i>Baseline score, mean (SD)</i> G1: 48.9 (12.6) G2: 42.7 (7.5)</p> <p><i>Other:</i> QALYs</p> <p><i>Six month QALY gain, mean (SD)</i> G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p><i>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</i></p> <p><i>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This</i></p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>episodes in patients referred for ECT</p> <p><i>Quality Rating</i> Good</p>	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 		<p><i>BDI:</i> Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD) NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	<p>suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales</p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>(verbal fluency, anterograde memory, and retrograde memory)</p> <p><i>MMSE</i> <i>Baseline n</i> G1: 16 G2: 22</p> <p>Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9)</p> <p>Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)</p> <p>Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3)</p> <p>Change, mean (SD): G1: 1.3 G2: -1.3 P < 0.08</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Attrition Overall to end of treatment 6/46, at 6 months 9/46</p> <p>At end of treatment, % G1: 6/24 G2: 0</p> <p>At end of follow-up, % NR Withdrawals due to efficacy, % G1: 5/24 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p> <p>Adherence/ compliance NR</p>
<p><i>Author, Year</i> O'Connor, 2003⁶⁴</p> <p><i>Country, setting</i> United States, University Hospital, inpatient vs. outpatient population not clearly reported</p> <p><i>Funding</i> NIH/NIMH and a NARSAD grant</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 28</p> <p><i>Duration</i> • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks).</p>	<p><i>TRD definition</i> • Patients referred for ECT • AD failures not required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Met criteria for MDD • HRSD > 18</p> <p><i>Exclusion criteria</i> • Psychosis, acute suicidality, other</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5)</p> <p>Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time <i>P</i> < 0.01</p>	<p><i>Quality of Life</i></p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning)</p> <p>Baseline n G1: 14 G2: 14</p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i> Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition</p> <p><i>Quality Rating</i> Fair</p>	<ul style="list-style-type: none"> Patients assessed for follow-up 2 weeks post txt <p><i>Medications allowed</i> rTMS patients completed a washout of all psychotropic medications while ECT continued all medications</p> <p><i>Strategy</i> Switch strategy for rTMS and augment or add-on strategy for ECT group</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Parameters</i> ECT</p> <ul style="list-style-type: none"> % receiving bilateral: 0 Intensity: 2.5 times seizure threshold Number of sessions (range, mean, SD): 6-12, 3/wk <p>rTMS</p> <ul style="list-style-type: none"> Frequency (Hz): 10 Motor threshold (%): 90 Number of trains: 20 Length of train (seconds): 8 	<ul style="list-style-type: none"> current Axis I diagnoses in DSM IV known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology personal or first degree family history of a seizure disorder inability to give informed consent 	<p><i>HAM-D</i> Baseline n Completers G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) $P = 0.001$</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)</p>	<p>Responders, n G1: NR G2: 0</p> <p>Remitters, n G1: NR G2: 100%</p> <p><i>Other</i> Validated measure Yes</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)</p> <p>Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with 2 week follow-up results ($P > 0.05$)</p>	<p>Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09)</p> <p>Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00)</p> <p>Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: $P > 0.05$ G2: 44.07 (10.43)</p> <p>RAVLT, Acquisition, mean (SD)</p> <p>Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09).</p> <p>End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) $P < 0.01$.</p> <p>Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) $P > 0.05$.</p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks 			<p>No significant interaction between treatment sessions and groups with respect to LN ($P > 0.05$)</p>	<p>RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD)</p> <p>Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08)</p> <p>End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80)</p> <p>Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07).</p> <p>Transient News Events Test (TNET-measure of retrograde memory)</p> <p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12)</p> <p>Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33)</p> <p>Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12)</p>

Evidence Table 16. KQ 4. Cognitive Functioning: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$.</p> <p>Cognitive function/memory impairment reported as primary outcome measures.</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % No attrition</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰</p> <p><i>Country, setting</i> USA, Single center, University department of psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good</p> <p>Fair for KQ2 and subgroups 11 (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint</p> <p><i>Interventions</i> G1: High-left TMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazepines G1: 26% vs. G2: 24%)</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥ 3 on ATHF) • Failures not required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence within past 2 years,</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p><i>Baseline n</i> G1: 35 G2: 33</p> <p><i>Treatment Failure</i></p> <p>Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67)</p> <p>Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 44.3 G2: 44.2</p> <p><i>Sex, % females</i> G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 15.7 G2: 19.8</p> <p>Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time $P = 0.002$</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) $P = 0.008$</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) $P = 0.033$</p> <p>No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse)</p> <p><i>BDI</i> Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33).</p> <p>The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 ($t = 4.24, P < 0.001$).</p> <p>Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms. (Data = NR)</p>

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> • Identical stimulation parameters • Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> • antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity 	<p>Groups similar at baseline Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>	<p>Random Regression analyses revealed significant group by time interaction ($P = 0.003$)</p>	<p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS11: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$) no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures. There was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated with TMS treatments. GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session.</p> <p><i>MMSE</i> NR</p>

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

					<p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Bretlau, 2008⁴¹</p> <p><i>Country, setting</i> Denmark, setting NR, outpatients</p> <p><i>Funding</i> Commercial source—please list name.supported by Medicin Valley Academy and an unrestricted research grant from H Lundbeck A/S</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 49</p> <p><i>Duration</i> 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. Escitalopram was administered during the entire trial at 20mg</p>	<p><i>TRD definition Required to be in current episode</i> Yes</p> <p><i>Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Aged 18 - 75 years; • meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); • failed to respond to at least one previous 	<p><i>Subgroups</i> No sub-group analysis</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: 100 G2: 100</p> <p><i>Failed 2 or more, %</i> G1: NR G2: NR</p> <p>Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9)</p>	<p><i>HAM-D</i> Yes HAM-D 17 Other, please describe.HAM-D 6 G1: rTMS + escitalopram G2: sham TMS + escitalopram</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall NR</p> <p>Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00</p> <p>Cardiovascular adverse events, % G1: palpitations: 3wk/ 12 wk mean: 0.23/0.14</p>

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

<p><i>Research Objective</i> To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment phase.</p> <p><i>Quality Rating</i> Fair</p>	<p>daily (10 mg daily for first wk of trial). Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals.</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n = 24) G1: rTMS + escitalopram G2: sham TMS + escitalopram G1: rTMS + escitalopram** G2: sham TMS + escitalopram**</p> <p><i>Parameters</i> • Location = Left Dorsolateral prefrontal cortex • Frequency = 8 Hz • Intensity = 90% motor threshold • Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. • Number of sessions = 15</p>	<p>adequate (at least 6 weeks) antidepressant treatment during the current episode;</p> <ul style="list-style-type: none"> • subjects with heart disorders or diabetes were included if they were in a somatically stable phase <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders; • potential risk factors for escitalopram such as hypersensitivity to the Intervention, • intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, • pregnancy or insufficient contraception in females of reproductive age; • risk factors for TMS such as history of epilepsy, • metal implants in the head or neck regions, • pacemaker or other electronic implants, • receiving antipsychotics; • having major suicide ideation. 	<p>Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: NR G2: NR</p> <p>Bipolar I G1: NR G2: NR</p> <p>Bipolar II G1: NR G2: NR</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 53.1 G2: 57.8</p> <p><i>Sex, % females</i> G1: 68% G2: 57%</p> <p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Not Specified, %</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR</p> <p>Groups similar at baseline Yes</p> <p><i>Tier</i></p>	<p>Baseline score, mean (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5)</p> <p>Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1), Awk3 = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2)</p> <p>Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2</p> <p>Responders, n G1: NR G2: NR</p>	<p>G2: 0.30/0.12</p> <p>Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22</p> <p>Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06</p> <p>Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39</p> <p>Somnolence, % NR</p> <p>Suicidality, % NR</p> <p>Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (P <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse</p>
--	--	---	---	--	---

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

	<p><i>Strategy</i> Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment</p>		<p>Tier 22A: 1+ failed, MDD</p>	<p>Remitters, n G1: NR G2: NR</p> <p>Other The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favour of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.83 (0.22-1.44), P = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.78 (0.18 - 1.39), P = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.48(-0.12 - 1.07), P = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.64 (0.04 - 1.24), P = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.47 (- 0.11 - 1.07), P = 0.22; HAM-D6 Awk 2 Effect size (95% CI) and</p>	<p>events include: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3</p>
--	---	--	---------------------------------	--	--

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				<p>Mann-Whitney P: 0.73 (.018 -1.39), P = 0.05; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.80 (0.20 - 1.42), P = 0.01; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.09 -1.29), P = 0.02; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney P:0.50 (-0.10 -1.09), P = 0.10; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.0.50 (- 0.10 - 1.09), P = 0.09;</p> <p>BDI G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p> <p>Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0)</p> <p>Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7),</p>	<p>= 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NR</p> <p>Predefined Yes</p> <p>MMSE No NR</p> <p>Baseline n NR</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) NR</p> <p>Other <i>Other</i> Yes Study utilized the UKU scale as listed before - Other adverse events include:</p>
--	--	--	--	--	--

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				<p>FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9) Change, mean (SD) G1: 12.4 G2: 9.4</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann- Whitney P = 0.73 (0.12 - 1.33), P = 0.03; Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.84 (0.24 -1.46), P = 0.00; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.64(0.02 -1.22), P = 0.03; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.04 - 1.24), P = 0.03; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.46 (-0.12 - 1.06), P</p>	<p>tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 =0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk</p>
--	--	--	--	---	---

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				<p>= 0.12;</p> <p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> NR</p> <p>Instrument Major Depression Inventory (MDI)</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p> <p>Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6)</p> <p>Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7) G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8)</p>	<p>12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p>Adequate information Yes <i>Attrition</i> Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out.</p> <p>At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0</p> <p>At end of follow-up, % G1: 21% G2: 4%</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> NR</p>
--	--	--	--	---	---

Evidence Table 17. KQ 4. Adverse Events : Tier 1 (rTMS vs. sham—MDD only) (continued)

				<p>Change, mean (SD) G1: 17.4 G2: 14.4 MDI Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.36 (-0.23 - 0.94), P = 0.18; Awk 3 Effect size (95% CI) and Mann-Whitney P:0.43 (-0.16 - 1.03), P = 0.29; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.29 (-0.29 - 0.88), P =0.20; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.22 (-0.36 - 0.81), P = 0.72; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.23 (-0.36 -0.81), P = 0.43;</p>	
--	--	--	--	--	--

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Rush et al., 2005²⁴,</p> <p><i>Country, setting</i> US, multicenter, outpatient psychiatric</p> <p><i>Funding</i> Cyberonics, Inc.</p> <p><i>Research Objective</i> To compare adjunctive VNS to sham in TRD patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> m-ITT/PP for efficacy, ITT for Aes</p> <p><i>N</i> 235</p> <p><i>Duration</i> 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt</p> <p><i>Interventions</i> G1: VNS G2: Sham</p> <p><i>Medications allowed</i> pts allowed up to 5 antidepressants, mood stabilizers, or other psychotropic medications</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disorder, suicidality • risks related to surgical implantation 	<p><i>Treatment Failure</i></p> <p>Percent with 4-6 current episode failures</p> <p>G1: 46.5% G2: 40.0%</p> <p><i>Polarity, %</i></p> <p>Unipolar G1: 88.4 G2: 90.9</p> <p>Bipolar I G1: 5.4 G2: 3.6</p> <p>Bipolar II G1: 6.3 G2: 5.5</p> <p><i>Age, mean yrs</i> G1: 47.0 G2: 45.9</p> <p><i>Sex, % females</i> G1: 59 G2: 66</p> <p><i>Race, % white</i> G1: 97 G2: 96</p> <p><i>HAM-D24</i> Baseline n G1: 119 G2: 116</p>	<p><i>HAM-D24</i></p> <p>N analyzed G1: 112 G2: 110</p> <p>Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) P = 0.639</p> <p>Responders, n G1: 17 (15.2%) G2: 11 (10.0%) P = 0.251</p> <p><i>MADRS</i> Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) P = 0.208</p> <p>Responders, n G1: 17 (15.2) G2: 12 (0.0) P = 0.378</p> <p><i>IDS</i> Endpoint score, mean (SD) NR</p>	<p><i>Quality of Life</i> Medical Outcomes Study Short Form-36 (MOS-SF36)</p> <p>Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2)</p> <p>Other Physical component between VNS and sham: P = 0.480, Mental Component between VNS and sham: P = 0.406</p>

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> On/Off cycle parameters: 30 sec on and 5 min off <p>Sham:</p> <ul style="list-style-type: none"> Device implanted but not turned on 		<p>Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2)</p> <p>MADRS Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3)</p> <p>IDS Baseline n G1: 112 (115 randomized) G2: 110</p> <p>Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5)</p> <p>CGI-I Baseline n G1: 112 G2: 110</p>	<p>% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) <i>P</i> = 0.158</p> <p>Responders, n G1: 19 (17) G2: 8 (7.3) <i>P</i> = 0.032</p> <p>Remitters, n NR</p> <p>CGI-I Endpoint score, mean (SD) NR</p> <p>Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, <i>P</i> = 0.648</p>	<p><i>Adverse Events</i> Overall, % NR</p> <p>Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3 Other:–</p> <ul style="list-style-type: none"> voice alteration: 68% v 38% cough increased: 29% v 9% dyspnea: 23% v 14%, dysphagia: 21% v 11%, neck pain: 21% v 10%, paresthesia: 16% v 10%, vomiting: 11% vs. 12%, laryngismus 11% v 2%, dyspepsia 10 v 5 wound infection 8% v 2%, hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% <p>Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11</p>

Evidence Table 18. KQ 4. Adverse Events : Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>patients, were cases of worsening depression requiring hospitalization</p> <p>Cardiac SAEs during implantation: 1.7% v 0%</p> <p>COSTART used to code reported events</p> <p><i>Attrition</i></p> <p>Overall, % 1.3 (3/235)</p> <p>At end of treatment, % G1: 2.6 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 2.6 G2: 0 9 pts had a protocol violation post randomization</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 19. KQ 4. Adverse Events : Tier 2 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Berman et al., 2000²⁸</p> <p><i>Country, setting</i> US, urban community health center, inpatient and outpatients</p> <p><i>Funding</i> Veterans Administration, NIMH, State of CT</p> <p><i>Research Objective</i> To assess efficacy of rTMS in unmedicated TRD patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> 2 weeks (10 weekdays of txt)</p> <p><i>Primary outcome =</i> HAM-D at 2wks</p> <p><i>Interventions</i> G1: rTMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20</p>	<p><i>TRD definition</i> • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imipramine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Current Major depressive episode (via Ham-D)</p> <p><i>Exclusion criteria</i> • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control</p>	<p><i>Treatment Failure</i> Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 augmentation in eachgroup)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 90</p> <p>Bipolar II G1: 0 G2: 10</p> <p><i>Age, mean yrs</i> G1: 45.2 G2: 39.4</p> <p><i>Sex, % females</i> G1: 20 G2: 40</p> <p><i>Race, % white</i> G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic)</p> <p><i>HAM-D 25</i> Baseline n G1: 10 G2: 10</p>	<p><i>HAM-D 25</i> G1: rTMS G2: Sham TMS</p> <p>Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4</p> <p>*Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) <i>P</i> < 0.05</p> <p>Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 <i>P</i> = 0.09 Three partial responders symptom severity returned to baseline within 1-2 weeks</p> <p><i>BDI</i> Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) <i>P</i> = 0.27</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, n G1: 60 G2: 50</p> <p>Difficulty starting urination great in active group <i>P</i> = 0.03</p> <p>Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) • Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appetit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or</p>

Evidence Table 19. KQ 4. Adverse Events : Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 2 • Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days <p>Sham</p> <ul style="list-style-type: none"> • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp 		<p>Baseline score, mean (SD)</p> <p>G1: 37.1</p> <p>G2: 37.3</p>		<p>lightheadedness, poor coordination, and muscle stiffness</p> <p><i>MMSE</i></p> <p>NR</p> <p><i>Attrition</i></p> <p>Overall, %</p> <p>15</p> <p>At end of treatment, %</p> <p>G1: 0.0</p> <p>G2: 30.0</p> <p>At end of follow-up, %</p> <p>G1: NA</p> <p>G2: NA</p> <p>Withdrawals due to efficacy, %</p> <p>G1: 0</p> <p>G2: 30</p> <p>Withdrawals due to adverse events, %</p> <p>G1: 0</p> <p>G2: 0</p> <p><i>Adherence/ compliance</i></p> <p>NR</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> McLoughlin et al., 2007⁷ Eranti et al., 2007⁸ Knapp et al., 2008⁹</p> <p><i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital in Invicta Mental Health Trust in Kent, 65.2% were inpatients</p> <p><i>Funding</i> National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating major depressive</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters) Type of analysis m-ITT</p> <p><i>N</i> 46</p> <p><i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p> <p><i>Strategy</i> Augmentation</p>	<p><i>TRD definition</i> • All patients referred for ECT: • No failure required <i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Right handed patients • more than 18 years old • referred for ECT due to major depressive episode</p> <p><i>Exclusion criteria</i> • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.</p>	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91</p> <p>Bipolar G1: 8.33% G2: 9.09 %</p> <p><i>Age, mean yrs</i> G1: 63.6 G2: 68.3</p> <p><i>Sex, % females</i> G1: 67.7 G2: 72.7</p> <p><i>Right handed, %</i> Overall: 100%</p> <p><i>HAM-D 17</i> Baseline n G1: 22 G2: 24</p> <p>Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)</p>	<p><i>HAM-D 17</i> Analyzed n G1: 22 G2: 23</p> <p>Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 <i>P</i> = 0.002, effect size of 1.44</p> <p>Follow-up at 6 months G1: NR G2: NR <i>P</i> = 0.93</p> <p>Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 <i>P</i> = 0.017</p> <p>Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p>Remitters, n HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22</p> <p>Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5)</p> <p>Other: QALYs</p> <p>Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</p> <p>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>episodes in patients referred for ECT</p> <p><i>Quality Rating</i> Good</p>	<p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 		<p><i>BDI:</i> Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD) NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	<p>suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>(verbal fluency, anterograde memory, and retrograde memory)</p> <p>MMSE Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9)</p> <p>Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)</p> <p>Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3)</p> <p>Change, mean (SD) G1: 1.3 G2: -1.3 $P < 0.08$</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p> <p>Attrition Overall to end of treatment 6/46, at 6 months 9/46</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>At end of treatment, % G1: 6/24 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 5/24 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> O'Connor, 2003⁶⁴</p> <p><i>Country, setting</i> United States, University Hospital, inpatient vs. outpatient population not clearly reported</p> <p><i>Funding</i> NIH/NIMH and a NARSAD grant</p> <p><i>Research Objective</i> Two procedures for treating major depressive disorder were compared with regard to their</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 28</p> <p><i>Duration</i> • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt</p> <p><i>Medications allowed</i></p>	<p><i>TRD definition</i> • Patients referred for ECT • AD failures not required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Met criteria for MDD • HRSD > 18</p> <p><i>Exclusion criteria</i> • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2</p> <p><i>HAM-D</i> Baseline n Completers G1: 14 G2: 14</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5)</p> <p>Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time $P < 0.01$</p> <p>Responders, n G1: NR G2: 0</p>	<p><i>Quality of Life</i> <i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning)</p> <p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09)</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>respective effects on mood and cognition</p> <p><i>Quality Rating</i> Poor</p>	<p>rTMS patients completed a washout of all psychotropic medications while ECT continued all medications</p> <p><i>Strategy</i> Switch strategy for rTMS and augment or add-on strategy for ECT group</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Parameters</i> ECT <ul style="list-style-type: none"> • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12 rTMS <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600 </p>	<ul style="list-style-type: none"> • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent 	<p>Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) <i>P</i> = 0.001</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)</p>	<p>Remitters, n G1: NR G2: 100%</p> <p><i>Other</i> Validated measure Yes</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)</p> <p>Change, mean (SD) At two weeks</p> <p>ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with 2 week follow-up results (<i>P</i> > 0.05)</p> <p>No significant interaction between treatment sessions and groups with respect to LN (<i>P</i> > 0.05)</p>	<p>Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00)</p> <p>Change, mean (SD) G1: 46.92 (10.80) Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: <i>P</i> > 0.05 G2: 44.07 (10.43)</p> <p>RAVLT, Acquisition, mean (SD)</p> <p>Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09).</p> <p>End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) <i>P</i> < 0.01.</p> <p>Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) <i>P</i> > 0.05.</p> <p>RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD)</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Total number of sessions:5/wk over 2wks 				<p>Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08)</p> <p>End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80)</p> <p>Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07).</p> <p>Transient News Events Test (TNET-measure of retrograde memory)</p> <p>Baseline n G1: 14 G2: 14 Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12)</p> <p>Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33)</p> <p>Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12)</p> <p>Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp</p>

Evidence Table 20. KQ 4. Adverse Events: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>and txt session: $P < 0.001$.</p> <p>Cognitive function/memory impairment reported as primary outcome measures.</p> <p>MMSE NR</p> <p><i>Attrition</i> Overall, % No attrition</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Schulze-Rauschenbach et al., 2005⁶³</p> <p><i>Country, setting</i> Germany, Psychiatric University Hospital, inpatients</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> To compare neurocognitive effects of unilateral ECT and rTMS using a control</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Observational study of patients completing txt</p> <p><i>N</i> 30</p> <p><i>Duration</i> Not clear- testing took place 8.8 days on average after last treatment Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks.</p> <p><i>Interventions</i> Control G1: ECT G2: rTMS</p> <p><i>Medications Allowed</i> Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study</p>	<p><i>TRD definition</i> • Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks • Not required or not specified to be in current episode</p> <p>Tier 1</p> <p><i>Inclusion criteria</i> • Consecutively admitted patients with DSM–IV diagnosis of MDD • Age over 18 years</p> <p><i>Exclusion criteria</i> • Previous treatment with ECT or rTMS • Additional Axis I diagnosis</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 46.7 G2: 47.7</p> <p><i>Sex, % females</i> G1: 50 G2: 44</p> <p>HAM-D 17 Baseline n G1: 14 G2: 16</p> <p>Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5)</p> <p>BDI Baseline n G1: 14 G2: 16</p> <p>SSMQ Baseline n G1: 14 G2: 16</p>	<p>HAM-D 17 Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9)</p> <p>Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, <i>P</i> = NS</p> <p>Responders, n G1: 6 (46%) G2: 7 (44%) <i>P</i> = 0.90</p> <p>BDI Change, mean (SD) G1: 7.6 G2: 6.4 Group x time, <i>P</i> = NS</p> <p>SSMQ</p> <p>Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8)</p> <p>Change, mean (SD) G1: 5.5 G2: 20.6</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included.</p> <p><i>Neuropsychological or executive functioning</i> Test scores ECT Pre / Post vs. rTMS Pre / Post Post; <i>P</i> = Post Ect vs. Post rTMS</p> <p>Learning and anterograde memory AVLT Immediate recall (trials 1-5); <i>P</i> = NS Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); <i>P</i> < 0.01 Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); <i>P</i> < 0.05 Recognition hits; <i>P</i> = NS and false alarms; <i>P</i> = NS MPT</p>

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> ECT: <ul style="list-style-type: none"> • % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) rTMS <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: • Total number of sessions: 2-3/wk <i>Strategy</i> Augment or add-on </p>		Baseline score, mean (SD) G1: -20.7 (19.0) G2: -16.8 (16.9)		Recall trial; <i>P</i> = NS and Delayed recall; <i>P</i> = NS Retrograde memory Retrograde AVLT Recall; <i>P</i> = NS and Recognition hits; <i>P</i> = NS Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); <i>P</i> < 0.05 Four-card task Free recall 2.0 (1.4) / 0.4 (0.5) vs. 1.4 / (1.2); <i>P</i> < 0.05 Recognition; <i>P</i> = NS AMI Recall score; <i>P</i> = NS Subjective memory SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); <i>P</i> < 0.05 Other cognitive functions MMSE; <i>P</i> = NS, TrailMakingTest A; <i>P</i> = NS, TrailMakingTest B; <i>P</i> = NS, Digit span (WAIS-R); <i>P</i> = NS, Letter-number span; <i>P</i> = NS, Word fluency (LPS); <i>P</i> = NS MMSE

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>G1: ECT G2: rTMS Recognition G3: Control</p> <p>Baseline n G1: 14 G2: 16 G3: 15</p> <p>Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0)</p> <p>Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1)</p> <p>Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01</p> <p>Other P = NS</p> <p><i>Attrition</i> Overall, % 3.3</p> <p>At end of treatment, % G1: 7 G2: 0</p>

Evidence Table 21. KQ 4. General Tolerability: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>At end of follow-up, % G1: NR G2: NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 0</p> <p>Withdrawals due to adverse events, % G1: 7 G2: 0 One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included in analysis</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰</p> <p><i>Country, setting</i> USA, Single center, University, Department of Psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good Fair for KQ2 and subgroups¹¹ (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint</p> <p><i>Interventions</i> G1: High-left TMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazepines G1: 26% vs. G2: 24%)</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥ 3 on ATHF) • Failures not required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence Within past 2 years,</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p><i>Baseline n</i> G1: 35 G2: 33</p> <p><i>Treatment Failure</i></p> <p><i>Current episode failures, mean (SD)</i> G1: 1.46 (0.78) G2: 1.48 (0.67)</p> <p><i>Mean failed trials (SD)</i> G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 44.3 G2: 44.2</p> <p><i>Sex, % females</i> G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p>	<p>HAM-D 17 Endpoint score, mean (SD) G1: 15.7 G2: 19.8</p> <p>Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time P = 0.002</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) P = 0.008</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) P = 0.033</p> <p>No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse)</p> <p>BDI Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 (t = 4.24, P < 0.001). Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms. (Data = NR)</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Those stopping medications had to be medication-free for at least 2 weeks • All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 32 • Length of train (seconds): 5 • Inter-train interval: 25-30 • Pulses per session: 1600 • Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> • Identical stimulation parameters • Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> • antisocial or borderline personality disorder, • active suicidal ideation • current symptoms of psychosis, • Hx of seizure disorder, • Hx of closed head injury with loss of consciousness or prior brain surgery • any other major psychiatric or medical comorbidity 	<p>Groups similar at baseline Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>	<p>Random Regression analyses revealed significant group by time interaction (P = 0.003)</p>	<p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS¹¹: At 15th session pain TMS 33% vs, sham 3% (P < 0.05) no statistically significant (P > 0.05) time by treatment group interactions for any of neuropsychological test measures., There was significant improvement in individual neuropsychological test performances for both groups. No confusion was associated withTMS treatments.GOAT assessments were well within normal range and ranged from 98 to 100. No significant (P > 0.05) differences between groups for any session.</p> <p>MMSE NR</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR Very unclear as to when patients discontinued</p> <p><i>Adherence/ compliance</i> NR</p>
<p><i>Author, Year</i> Garcia-Toro et al., 2006¹⁷</p> <p><i>Country, setting</i> Spain, single center, all outpatients</p> <p><i>Funding</i> Fundacio La Marato de TV3</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in analysis</p> <p><i>N</i> 30</p> <p><i>Duration</i> • Primary outcome after 2 weeks of active</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Failed 2+ txt trials at 4+ weeks Not required or not specified to be in current episode <p>Tier 1</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> At least 18 yrs old, MDD, unipolar 	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar</p> <p>100%</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD)</p> <p>At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10)</p> <p>At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18) G3: 18.10 (6.15)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in pharmacotherapy</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i> To assess the efficacy of high and low frequency rTMS and different locations of activation</p> <p><i>Quality Rating</i> Fair</p>	<p>treatment</p> <ul style="list-style-type: none"> Follow-up: 2 weeks post treatment <p><i>Interventions</i> G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam)</p> <p><i>Medications allowed</i> All pts continued (failed) AD medication and other psychotropic meds</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS Low: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session: 1800</p>	<p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Contraindications for rTMS and high suicide risk 	<p><i>Age, mean yrs</i> G1: 47.2 G2: 48.5 G3: 51.1</p> <p><i>Sex, % females</i> G1: 70 G2: 40 G3: 40</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> G1: 90% G2: 100% G3: 100%</p> <p>HAM-D 21</p> <p>Baseline n G1: 10 G2: 10 G3: 10</p> <p>Baseline score, mean (SD) G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14)</p>	<p>Follow-up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0)</p> <p>Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%)</p> <p>At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), $P = 0.048$</p> <p>Follow-up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%) G1: vs. G2+G3, $P = 0.121$</p> <p>Responders, n (%) G1: 0 (0) G2: 2 (20) G3: 2 (20) $P = NR$</p>	<p>At end of treatment, % G1: 0 G2: 0 G3: 0</p> <p>At end of follow-up, % NR Does not report which group 3 patients came from</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission computed tomography (20- At end of treatment, % G1: 0 G2: 0 G3: 0</p> <p>At end of follow-up, % NR Does not report which group 3 patients came from</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Total number of sessions: 10 in 2 wks <p>High</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval: 20+5 • Pulses per session: 1200 • Total number of sessions: 10 in 2 wks <p>Sham</p> <ul style="list-style-type: none"> • Same but with coil angling 45 degrees away from scalp 		<p>CGI-S</p> <p>Baseline n</p> <p>G1: 10</p> <p>G2: 10</p> <p>G3: 10</p> <p>Baseline score, mean (SD)</p> <p>G1: 4.7 (0.82)</p> <p>G2: 4.8 (1.0)</p> <p>G3: 4.8 (0.63)</p>	<p>CGI-S</p> <p>Endpoint score, mean (SD)</p> <p>At 2 weeks</p> <p>G1: 4.6 (0.97)</p> <p>G2: 3.8 (1.48)</p> <p>G3: 3.9 (0.99)</p> <p>2 week follow-up</p> <p>G1: 4.75 (1.16)</p> <p>G2: 4.00 (1.15)</p> <p>G3: 3.7 (1.57)</p>	<p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission computed tomography (20-Hz rTMS to an area of relatively low activity and 1-Hz rTMS to an area showing relatively high activat</p> <p><i>Adherence/ compliance</i></p> <p>Compliance</p> <p>all patients completed active 2 week treatment</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Holtzheimer et al., 2004¹⁹</p> <p><i>Country, setting</i> USA, single center, outpatient/inpatient status not clearly stated</p> <p><i>Funding</i> University of Washington</p> <p><i>Research Objective</i> Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p>N 15</p> <p><i>Duration</i> Primary endpoint following 2 weeks of treatment and follow-up 1 week after txt completed</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> All pts discontinued (failed) AD medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5</p>	<p><i>TRD definition</i> • Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18</p> <p><i>Exclusion criteria</i> • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy</p>	<p><i>Treatment Failure</i></p> <p>Failed 7 or more, % G1: 85.7 G2: 37.5</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 40.4 G2: 45.4</p> <p><i>Sex, % females</i> G1: 57.1 G2: 42.9</p> <p>Right handed, % G1: 100 G2: 100</p> <p>HAM-D 17 Baseline n G1: 7 G2: 8</p> <p>Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3)</p> <p>BDI Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)</p>	<p>HAM-D 17 Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7)</p> <p>At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)</p> <p>1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1)</p> <p>Change, mean (SD) At week 1 G1: 4.7 G2: 2.8</p> <p>At week 2 G1: 8.1 G2: 5.5</p> <p>1 week follow-up G1: 3.9 G2: 3.2 All endpoints, <i>P</i> = NS</p> <p>Responders, n (%) At week 1 G1: 0 G2: 0</p> <p>At week 2 G1: 2 (28.6) G2: 1 (12.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally tolerated.</p> <p><i>Neuropsychological or executive functioning</i> Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); <i>P</i> < 0.05).</p> <p>No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: 30-60 Pulses per session: 1600 • Total number of sessions: 10 over 2 wks <p>Sham rTMS</p> <ul style="list-style-type: none"> • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp 			<p>1 week follow-up G1: 0 G2: 0</p> <p>BDI Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)</p> <p>At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4)</p> <p>1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9)</p> <p>Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1</p> <p>Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), <i>P</i> = NS</p>	<p><i>MMSE</i> NR</p> <p>There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p> <p><i>Attrition</i> Overall, % 0 during treatment. 3 (20%) before final assessment at week 3</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % G1: 28.6 G2: 12.5</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p>

Evidence Table 22. KQ 4. General Tolerability: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<i>Adherence/ compliance</i> Compliance All 15 subjects completed all 10 txt sessions

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Boutros et al., 2002¹³</p> <p><i>Country, setting</i> US, Yale School of Medicine and VA-Connecticut, outpatient</p> <p><i>Funding</i> VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer</p> <p><i>Research Objective</i> To provide additional data on efficacy and safety for rTMS as an augment strategy in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 21</p> <p><i>Duration</i> 2 weeks txt; follow-up with responders for up to 20 weeks post txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> Pts allowed to continue all current psychotropic meds</p> <p><i>Strategy</i> Augmentation, 3 pts in active and 1 in sham txt were not on any meds</p> <p><i>Parameters</i> rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode</p> <p>Tier 1 Inclusion criteria • Major Depression • HAM-D25 >= 20</p> <p>Exclusion criteria • Suicidality • "Prominent" psychotic symptoms • History of neurological disorders • Current drug abuse</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 49.5 G2: 52.0</p> <p><i>Sex, % females</i> G1: 25 G2: 10</p> <p><i>Right handed, %</i> G1: 90.9 G2: 88.9</p> <p><i>HAM-D</i> Baseline n G1: 12 G2: 9</p> <p>Baseline score, mean (SD) G1: 34.4 (10.1) G2: 31.7 (4.9)</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11</p> <p>Change, mean (SD) G1: -11.75 G2: -6.22 P = NS</p> <p>Responders, n Defined as 30% improvement on HAM-D G1: 7 G2: 2</p> <p>Responders, n (%) Defined as 50% improvement on HAM-D G1: 3 G2: 2</p> <p><i>Relapse</i> Of 6 active treatment responders included in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in the 20-week follow-up, 1 relapsed</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6</p> <p>Cognitive impairment, % Difficulty concentrating (phase 1 only) G1: 25 G2: NR</p> <p>Headache, % "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR</p> <p><i>Attrition</i> Overall, % 18.2% (4/22)</p> <p>At end of treatment, % G1: 8.3 (1/12) G2: 30.0 (3/10)</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: 58 • Pulses per session: 800 • Total number of sessions: 10 over 10 weekdays Sham: <ul style="list-style-type: none"> • Coil angled 90 degrees to scalp • 1 wing of figure 8 touching scalp 				At end of follow-up, % NR Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Fitzgerald et al., 2006¹⁴</p> <p><i>Country, setting</i> Australia, single center</p> <p><i>Funding</i> Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT (LOCF)</p> <p><i>N</i> 50</p> <p><i>Duration</i> 2 wks double blind with those with >20% decrease in MADRS to continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • 2+ failed medications with txt duration ≥6 wks • Not required or not specified to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • DSM-IV diagnosis of Major Depressive Episode • MADRS ≥ 20 <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Significant medical illness 	<p><i>Treatment Failure</i></p> <p>Mean failed AD trials (lifetime)</p> <p>G1: 5.6 (3.1) G2: 6.2 (3.0)</p> <p><i>Polarity, %</i></p> <p>Unipolar G1: 84% G2: 84%</p> <p><i>Bipolar</i></p> <p>G1: 16% G2: 16%</p> <p><i>Age, mean yrs</i></p> <p>G1: 46.8 G2: 43.7</p>	<p><i>HAM-D 17</i></p> <p>Endpoint score, mean (SD) NR</p> <p>Change, % decrease (SD)</p> <p>G1: 45.2% (40.1) G2: 5.4% (23.1) <i>P</i> < 0.001</p> <p>Change, mean</p> <p>G1: -10.17 G2: -1.07</p> <p>Responders, n (%)</p> <p>At 6wks G1: 13 (52.0) G2: 2 (8.0) <i>P</i> = 0.001</p>	<p><i>Quality of Life</i></p> <p>GAF</p> <p>Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9)</p> <p>Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [<i>P</i> <0.05]</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i> rTMS versus placebo for depression</p> <p><i>Quality Rating</i> Fair</p>	<p>outcome after 2 and 6 weeks of txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications allowed</i></p> <ul style="list-style-type: none"> • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, • Antipsychotic medication, • Benzodiazepines <p><i>Strategy</i> Augmentation, 23% not taking medication at study entry</p> <p><i>Parameters</i> rTMS Low Right: Frequency (Hz):1</p> <ul style="list-style-type: none"> • Motor threshold (%): 110 • Number of trains: 3 • Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 <i>ategy</i> 	<ul style="list-style-type: none"> • Neurological disorders • Other axis I psychiatric disorders 	<p><i>Sex, % females</i> G1: 60 G2: 64</p> <p><i>HAM-D 17</i> Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4)</p> <p><i>BDI</i> Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9)</p> <p><i>MADRS</i> Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)<i>RS</i></p> <p>Baseline n</p>	<p>Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0)</p> <p><i>P = NR</i></p> <p><i>BDI</i></p> <p>Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7)</p> <p>At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8)</p> <p>At 6 weeks G1: 9.2 (6.7) G2: NR</p> <p>Change, mean (SD) At week 2 G1: 10.9 G2: 7.7</p> <p>At 4 weeks G1: 18.7 G2: 8.3</p> <p>At 6 weeks G1: 20.0 G2: NR, <i>P = 0.01</i></p>	<p>Change, mean (SD) G1: 10.2 G2: 1.1 GAF Scale (t=2.0, df=40.2, <i>P < 0.05</i>)</p> <p><i>Adverse Events</i> Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved on digit span backward test improved in rTMS only (group by time: <i>P = 0.07</i>). Controlled Oral Word Association test improved for both groups (time: <i>P = 0.001</i>). Nausea 12% vs. 0, No seizures or manic episodes;</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>Sequential High Left:</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 <p>• Total number of sessions: 10 sessions 5 days/wk</p> <p>Sham:</p> <ul style="list-style-type: none"> • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides) 			<p>Responders, n NR</p> <p>Remitters, n NR</p> <p><i>MADRS</i> Endpoint score, mean (SD)</p> <p>At week 2 G1: 26.2 (10.2) G2: 30.9 (8.2)</p> <p>At week 4 G1: 11.7 (7.1) G2: 34.5 (12.0)</p> <p>At week 6 G1: 8.9 (7.9) G2: NA</p> <p>Change, mean (SD) At week 2 G1: 7.8 G2: 3.2</p> <p>At week 4 G1: 22.3 G2: 0.4 (increased)</p> <p>At week 6 G1: 25.1 G2: NA</p>	<p><i>Neuropsychological or executive functioning</i> Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction Digit span backward Test Performance improved in rTMS only (group by time: <i>P</i> = 0.07). Controlled Oral Word Association Test Improved for both groups <i>P</i> = 0.001</p> <p><i>MMSE</i> NR</p> <p><i>Other</i> Nausea 12% vs. 0 No seizures or manic episodes;</p> <p><i>Attrition</i> Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Group by time, $P = 0.001$ at all time points</p> <p>Responders, n At 6 weeks G1: 11 G2: 2 $P < 0.05$</p> <p>Remitters, n</p> <p>MADRS < 10 At 6 weeks G1: 9 G2: 0 $P = 0.005$</p> <p>At week 2 G1: 2 G2: 0</p> <p>Follow-up at week 3 G1: 3 G2: 0</p> <p>Follow-up at week 4</p>	<p>After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn</p> <p>At end of treatment, % G1: 0 G2: 12</p> <p>At end of follow-up, % G1: 56 G2: 100</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Fitzgerald et al., 2003¹⁵</p> <p><i>Country, setting</i> Australia 2 general psychiatric services, outpatients</p> <p><i>Funding</i> National Health and Medical Research Council and a grant from Stanley Medical Research Institute</p> <p><i>Research Objective</i> To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 60</p> <p><i>Tier 1</i></p> <p><i>Duration</i> Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up assessment conducted at 2 weeks post txt.</p> <p><i>Interventions</i> G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham</p> <p><i>Medications Allowed</i> 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Failed a minimum of 2 courses of antidepressant medications (6+ weeks) <p>Not required or not specified to be in current episode</p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> DSM-IV diagnosis of Major Depression (included bipolar depression) <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders 	<p><i>Treatment Failure</i> Mean failed trials Overall (SD) 5.68 (3.40)</p> <p><i>Polarity, %</i> Bipolar I G1: 5 G2: 5 G3: 20</p> <p><i>Age, mean yrs</i> G1: 42.2 G2: 45.55 G3: 49.15</p> <p><i>Sex, % females</i> G1: 40 G2: 35 G3: 55</p> <p><i>Right handed, %</i> G1: 90 G2: 100 G3: 85</p> <p><i>BDI</i> Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)</p>	<p><i>BDI</i> Endpoint score, mean (SD)</p> <p>At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7)</p> <p>Change, mean (SD) At 2 weeks G1: -6.4 G2: -7.8 G3: -2.3 P = 0.03</p> <p><i>MADRS</i> Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5)</p> <p>Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) P = 0.004 G1: vs. G3, G2 vs. G3, P < 0.005</p>	<p><i>Quality of Life</i></p> <p>GAF Global Assessment of Functioning</p> <p>Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)</p> <p>Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8)</p> <p>Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5</p> <p>Overall group F56,2=2.6; P =.08; LFR-TMS vs. sham: P = 0.03; and HFLTMS vs. sham: P = 0.09</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS LowFrequency (Hz):1</p> <ul style="list-style-type: none"> • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week <p>rTMS High</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week 		<p><i>MADRS</i> Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)</p>	<p>Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) <i>P</i> = 0.07</p> <p>Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 <i>P</i> = NR</p> <p><i>CGI</i> Endpoint score, mean (SD) NR <i>P</i> =.01</p>	<p><i>Quality of Life</i> Overall group F56,2=2.6; <i>P</i> =.08; LFR-TMS vs. sham: <i>P</i> = 0.03; and HFLTMS vs. sham: <i>P</i> = 0.09</p> <p><i>Adverse Events</i> Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. Although there was no difference in incidence of these adverse effects (<i>P</i> =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	Sham rTMS • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week				Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: One patient withdrew after 1 session of HFL-TMS treatment in single-blind phase of study owing to site pain. One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium <i>Neuropsychological or executive functioning</i> • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<ul style="list-style-type: none"> • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on verbal paired associates (t50=-7.3; P < 0.001), verbal fluency (t48=-3.8; P < 0.001), and digit span forwards (t48=-1.8; P = 0.003) subscales; Personal Semantic Memory Schedule (t50=-2.4; P = 0.02); and Autobiographical Memory Schedule (t50=-1.9; P = 0.05). • A similar pattern of improvements was seen for each of treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Inventory scores across same times.</p> <p><i>MMSE</i> NR</p> <p><i>Other</i></p> <p><i>Attrition</i> Overall, % None in initial 2 week treatment phase</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % NR But at least 28.3% did not continue on thru 2nd 2 weeks</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Su et al., 2005²⁶</p> <p><i>Country, setting</i> Taiwan, NS</p> <p><i>Funding</i> Taipei Veterans General Hospital, patient status not reported</p> <p><i>Research Objective</i> To investigate whether two weeks of rTMS applied to LDLPFC can alleviate TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 33</p> <p><i>Duration</i> 2wk of active txt Primary outcome: HAM-D at 2 weeks (after 10 txt)</p> <p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: 20Hz rTMS (N analyzed = 10) G2: 5Hz rTMS (N analyzed = 10) G3: Sham (N analyzed = 10)</p> <p><i>Medications allowed</i> pts allowed to continue all meds constant for 4 weeks prior (e.g. antidepressants, antipsychotics, mood stabilizers, or stimulant)</p>	<p><i>TRD definition</i> • TRD (2+ failed adequate trials) • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major Depressive Episode or Bipolar (DSV-IV), • Ham-D21 score >=18</p> <p><i>Exclusion criteria</i> • history of - epilepsy, • any physical and neurological abnormalities, major head trauma, • psychotic symptoms; • current use of a pacemaker, • suicidality</p>	<p><i>Subgroups</i> Ethnicity - Chinese, females by menopausal status</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 90 G2: 80 G3: 80</p> <p>Bipolar G1: 10 G2: 20 G3: 20</p> <p>Bipolar II G1: 10 G2: 10 G3: 10</p> <p><i>Age, mean yrs</i> G1: 43.6 G2: 43.2 G3: 42.6</p> <p><i>Sex, % females</i> G1: 70 G2: 80 G3: 70</p>	<p><i>HAM-D 17</i> N analyzed G1: 10 G2: 10 G3: 10</p> <p>Endpoint score, mean (SD) At 2 weeks G1: 12.8(6.7) G2: 12.3(7.7) G3: 19.0(7.7)</p> <p>Change, mean (SD) At 2 weeks G1: -13.4(4.9) G2: -14.2(6.0) G3: -3.7(9.3) G1: vs. G3, G2 vs. G3 <i>P</i> < 0.01</p> <p>Responders, n G1: 6 (60) G2: 6 (60) G3: 1 (10) G1: + G2 vs. G3 <i>P</i> = 0.01</p> <p>Remitters, n Ham-D17<= 7 G1: 5 (50) G2: 5 (50) G3: 0</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 20 (n=2) G2: 20 (N=2) G3: 11.1 (N=1) Pain at rTMS site: 16.7% withdrew due to pain at stimulation site SEE AE section</p> <p><i>Attrition</i> Overall, % 9.1 (3/33)</p> <p>At end of treatment, % G1: 0 G2: 16.7 G3: 9.1</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 0 G3: 9.1</p> <p>Withdrawals due to adverse events, % G1: 0 G2: 16.7 G3: 0</p>

Evidence Table 23. KQ 4. General Tolerability: Tier 1 (rTMS vs . sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i></p> <p>Augmentation</p> <p><i>Parameters</i></p> <p>rTMS High:</p> <ul style="list-style-type: none"> • Frequency (Hz): 20 • Motor threshold (%): 100 • Number of trains:40 • Length of train (seconds):2 • Inter-train interval:28 • Pulses per session: 1600 • Total number of sessions: 5/wk or 10 in 10 weekdays <p>rTMS Low:</p> <ul style="list-style-type: none"> • Frequency (Hz): 5 • Motor threshold (%): 100 • Number of trains: 40 • Length of train (seconds): 8 • Inter-train interval: 22 • Pulses per session: 1600 • Total number of sessions:5/wk or 10 in 10 days <p>Sham:</p> <ul style="list-style-type: none"> • Same as high frequency rTMS. <p>Coil placed at 90 degrees off skull.</p>		<p><i>HAM-D 17</i></p> <p>Baseline N</p> <p>G1: 10</p> <p>G2: 12</p> <p>G3: 11</p> <p>Baseline score, mean (SD)</p> <p>G1: 23.2 (7.5)</p> <p>G2: 26.5 (5.2)</p> <p>G3: 22.7 (4.7)</p> <p><i>BDI</i></p> <p>Baseline score, mean (SD)</p> <p>G1: 28.0(9.1)</p> <p>G2: 33.9(7.6)</p> <p>G3: 33.4(9.6)</p> <p><i>CGI-S</i></p> <p>Baseline score, mean (SD)</p> <p>G1: 4.5(0.7)</p> <p>G2: 4.7(0.8)</p> <p>G3: 4.7(0.48)</p>	<p><i>BDI</i></p> <p>Endpoint score, mean (SD)</p> <p>At 2 weeks</p> <p>G1: 12.8(6.7)</p> <p>G2: 19.7(12.3)</p> <p>G3: 28.7(15.1)</p> <p>Change, mean (SD)</p> <p>At 2 weeks</p> <p>G1: 15.2(7.5)</p> <p>G2: 14.2(10.4)</p> <p>G3: 4.7(9.1)</p> <p>G1: vs. G3 $P < 0.05$</p> <p>G2 vs. G3 $P < 0.1$</p> <p><i>CGI-S</i></p> <p>Endpoint score, mean (SD)</p> <p>At week 2</p> <p>G1: 2.8(1.1)</p> <p>G2: 2.0(0.9)</p> <p>G3: 3.6(1.1)</p> <p>Change, mean (SD)</p> <p>G1: -1.7</p> <p>G2: -2.0</p> <p>G3: -1.1</p> <p>$P = NS$</p>	<p>1 dropped out of sham for worsening of clinical symptoms, this was categorized as LOE</p> <p><i>Adherence/ compliance</i></p> <p>NR</p>

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Rush et al., 2005²⁴ Carpenter et al., 2004²⁵</p> <p><i>Country, setting</i> US, multicenter, outpatient psychiatric</p> <p><i>Funding</i> Cyberonics, Inc.</p> <p><i>Research Objective</i> To compare adjunctive VNS to sham in TRD patients</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> m-ITT/PP for efficacy, ITT for Aes</p> <p><i>N</i> 235</p> <p><i>Duration</i> 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt</p> <p><i>Interventions</i> G1: VNS G2: Sham</p> <p><i>Medications allowed</i> pts allowed up to 5 antidepressants, mood stabilizers, or other psychotropic medications</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disorder, suicidality • risks related to surgical implantation 	<p><i>Treatment Failure</i></p> <p>Percent with 4-6 current episode failures G1: 46.5% G2: 40.0%</p> <p><i>Polarity, %</i></p> <p>Unipolar G1: 88.4 G2: 90.9</p> <p>Bipolar I G1: 5.4 G2: 3.6</p> <p>Bipolar II G1: 6.3 G2: 5.5</p> <p><i>Age, mean yrs</i> G1: 47.0 G2: 45.9</p> <p><i>Sex, % females</i> G1: 59 G2: 66</p> <p><i>Race, % white</i> G1: 97 G2: 96</p> <p><i>HAM-D24</i> Baseline n G1: 119 G2: 116</p>	<p><i>HAM-D24</i></p> <p>N analyzed G1: 112 G2: 110</p> <p>Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) P = 0.639</p> <p>Responders, n G1: 17 (15.2%) G2: 11 (10.0%) P = 0.251</p> <p><i>MADRS</i> Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) P = 0.208</p> <p>Responders, n G1: 17 (15.2) G2: 12 (0.0) P = 0.378</p>	<p><i>Quality of Life</i> Medical Outcomes Study Short Form-36 (MOS-SF36)</p> <p>Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2)</p> <p>Other Physical component between VNS and sham: P = 0.480, Mental Component between VNS and sham: P = 0.406</p>

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> On/Off cycle parameters: 30 sec on and 5 min off Duration of treatment: <p><i>Sham:</i></p> <ul style="list-style-type: none"> Device implanted but not turned on 		<p>Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2)</p> <p><i>MADRS</i> Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3)</p> <p><i>IDS</i> Baseline n G1: 112 (115 randomized) G2: 110</p> <p>Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5)</p> <p><i>CGI-I</i> Baseline n G1: 112 G2: 110</p>	<p><i>IDS</i> Endpoint score, mean (SD) NR</p> <p>% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) <i>P</i> = 0.158</p> <p>Responders, n G1: 19 (17) G2: 8 (7.3) <i>P</i> = 0.032</p> <p>Remitters, n NR</p> <p><i>CGI-I</i> Endpoint score, mean (SD) NR</p> <p>Achieving 1 or 2 score, % (SD) G1: 13.9 G2: 11.8 VNS v. Sham, <i>P</i> = 0.648</p>	<p><i>Adverse Events</i> Overall, % NR</p> <p>Cardiovascular adverse events, %</p> <p>G1: 5, palpitations 5 G2: 3</p> <p>Other:–</p> <ul style="list-style-type: none"> voice alteration: 68% v 38% cough increased: 29% v 9% dyspnea: 23% v 14%, dysphagia: 21% v 11%, neck pain: 21% v 10%, paresthesia: 16% v 10%, vomiting: 11% vs. 12%, laryngismus 11% v 2%, dyspepsia 10 v 5 wound infection 8% v 2%, hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% <p>Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116)</p>

Evidence Table 24. KQ 4. General Tolerability: Tier 1 (VNS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>12 events, involving 11 patients, were cases of worsening depression requiring hospitalization</p> <p>Cardiac SAEs during implantation: 1.7% v 0%</p> <p>COSTART used to code reported events</p> <p><i>Attrition</i></p> <p>Overall, % 1.3 (3/235)</p> <p>At end of treatment, % G1: 2.6 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 2.6 G2: 0</p> <p>9 pts had a protocol violation post randomization</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Stern et al., 2007³²</p> <p><i>Country, setting</i> NR, outpatient setting</p> <p><i>Funding</i> The Milton Fund, NARSAD, Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Ciencia</p> <p><i>Research Objective</i> To test hypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in the analysis</p> <p><i>N</i> 45</p> <p><i>Duration</i> • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse.</p> <p>Primary Outcome: HAM-D at 2 weeks and 2 weeks after treatment</p> <p><i>Interventions</i> G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz rTMS to right DLPFC G4: Sham rTMS</p> <p><i>Medications allowed</i> No psychotropic medications were allowed</p>	<p><i>TRD definition</i> • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20</p> <p><i>Exclusion criteria</i> • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100 % MDD</p> <p><i>Age, mean yrs</i> G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3</p> <p><i>Sex, % females</i> G1: 60 G2: 60 G3: 70 G4: 60</p> <p><i>Right handed, %</i> 100</p> <p><i>HAM-D 21</i></p> <p>Baseline n G1: 10 G2: 10 G3: 10 G4: 15</p> <p>Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD)</p> <p>At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5)</p> <p>At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6)</p> <p>Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3)</p> <p>Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3)</p> <p>Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, $P = 0.001$</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> 9/45 pts reported severe headaches (pts by group NR); no seizures</p> <p><i>Attrition</i> Overall, %: 17.8</p> <p>At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10</p> <p>At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20</p> <p>Withdrawals due to efficacy: NR</p> <p>Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period.</p>

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>rTMS</p> <p>High Frequency:</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 <p>Low Frequency</p> <p>LDLPFC:</p> <ul style="list-style-type: none"> • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 <p>Low Frequency</p> <p>RDLFPFC:</p> <ul style="list-style-type: none"> • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 	<ul style="list-style-type: none"> • H/O epilepsy or unprovoked seizures or other neurological disorder • Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy 	<p>G3: 27.9 (3.8) G4: 27.4 (2.9)</p>	<p>2 week follow-up</p> <p>G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, $P = 0.00001$</p> <p>Responders, n</p> <p>At week 1</p> <p>G1: 0 G2: 0 G3: 0 G4: 0</p> <p>At week 2</p> <p>G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>1 week follow-up</p> <p>G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>2 week follow-up</p> <p>G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0 G1/G3 vs. G2/G4 ($P < 0.0005$)</p>	<p>Reported in text as dropped out following week 2.</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 25. KQ 4. General Tolerability: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 <p>Sham rTMS:</p> <ul style="list-style-type: none"> • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above <p><i>Strategy</i> Switch Number of trains: 1</p> <ul style="list-style-type: none"> • Length of train 			<p>Remitters, n HAM-D ≤ 10</p> <p>At week 1 G1: 0 (0%) G2: 0 (0%)</p> <p>G3: 0 (0%) G4: 0 (0%)</p> <p>At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%)</p> <p>1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%)</p> <p>2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%)</p> <p>Responders followed for additional two weeks (endpoint 2wk follow-up)</p> <p>G1: vs. G3 P = NS (all times); G2 vs. G4 and G1: vs. G3 P = NS (all times)</p>	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Harley, 2008³⁶</p> <p><i>Country, setting</i> United States, university clinics, outpatient psychiatric</p> <p><i>Funding</i> Kaplan Fellowship Award Grant through Harvard Medical School</p> <p><i>Research Objective</i> To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 24</p> <p><i>Duration</i> Primary outcome after 16 weeks of active txt Follow-up: 6 months</p> <p><i>Interventions</i> G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control</p> <p><i>Medications Allowed</i> Patients continued antidepressant therapy</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1</p>	<p><i>TRD definition</i> • 1+ failed medications (6+ weeks at “standard effective dose”) • Not required or not specified to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study.</p> <p><i>Exclusion criteria</i> • Borderline personality disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.</p>	<p><i>Baseline N</i> G1: 13 G2: 11</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, % MDD</i></p> <p><i>Overall:</i> 100</p> <p><i>Age, mean yrs</i> Overall: 41.8</p> <p><i>Sex, % females</i> Overall: 75</p> <p><i>Race, % white</i> Overall: 83</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) P = NS</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) P = NS</p>	<p><i>HAM-D 17</i> Analyzed n G1: 10 G2: 9</p> <p>Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23)</p> <p>Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78</p> <p><i>P < 0.05 Remitters, n</i> Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) P = NR</p> <p><i>BDI</i> Endpoint score, mean (SD)</p> <p>At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30)</p> <p>Change, mean (SD) G1: -12.80 G2: -1.55 P < 0.01</p>	<p><i>Quality of Life Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT)</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24)</p> <p>Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69)</p> <p>Change, mean (SD) G1: -1.3 G2: -0.33 P = NS</p> <p><i>Social Adjustment Scale-Self-Report (SAS-SR) work subscale</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)</p>

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Total number of sessions:16 G2: Wait list 	<ul style="list-style-type: none"> Active suicidality requiring more intensive levels of care Severe or unstable medical conditions Previous or current CBT experience 			<p>Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66)</p> <p>Change, mean (SD) G1: -16.80 G2: 0.34 <i>P</i> < 0.05</p> <p><i>Adverse Events</i> NR MMSE NR</p> <p><i>Attrition</i> Overall, %: 21</p> <p>At end of treatment, % G1:23 G2:18</p> <p>At end of follow-up, % G1:20 G2: NR</p> <p>Withdrawals due to efficacy, % G1: 8 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p>

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue in study and a medical problem prevented second from continuing.</p> <p><i>Adherence/ compliance</i> Compliance Participants completed a weekly check-in form asking about medication compliance over preceding month. 19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had</p>

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Paykel, 1999³⁸ Scott, 2000⁵⁹</p> <p>Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219.</p> <p><i>Country, setting</i> UK, outpatient</p> <p><i>Funding</i> Medical Research Council, London, England and a grant from Oxford and Anglia Region</p> <p><i>Research Objective</i> To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintenance treatment with antidepressants.</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 158</p> <p><i>Duration</i> Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks.</p> <p><i>Interventions</i> G1: Clinical management Only G2: CT plus Clinical Management</p> <p><i>Medications allowed</i> Continued on current medications with dose adjustments allowed</p> <p><i>Strategy</i> Augmentation</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, Residual symptoms had lasted 2 to 18 months. Failure required to be in the current episode <p><i>Tier 2 Inclusion criteria</i></p> <ul style="list-style-type: none"> Unipolar depression, aged 21 to 65 years, 	<p><i>Treatment Failure</i> Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar 100% 100%</p> <p><i>Age, mean yrs</i> G1: 43.2 (11.2) G2: 43.5 (9.8)</p> <p><i>Sex, % females</i> G1: 53% G2: 46%</p> <p><i>HAM-D 17</i> Baseline n G1: 78 G2: 80</p> <p>Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)</p>	<p><i>HAM-D 17</i> G1: Clinical Management only G2: CT plus Clinical Management</p> <p>Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2)</p> <p>Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7)</p> <p>Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3)</p> <p>Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 P = NS</p> <p>Follow-up at 44 weeks G1: - 3.0 G2: -4.5</p> <p>Follow-up at 68 weeks G1: -5.0 G2: -4.9</p>	<p>forgotten a medication dose between 1 to 4 times in previous month.</p> <p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 20% did not adhere to protocol through to study end or relapse point</p> <p>At end of treatment, % G1: 4 G2: 14</p> <p>At end of follow-up, % G1: 12 G2: 10</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]</p>

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Quality Rating</i> Good</p>	<p><i>Parameters</i> Psychotherapy:</p> <ul style="list-style-type: none"> • Type of therapy: Cognitive Therapy • Method: Individual • Number of sessions/week: 1.25/wk • Total number of sessions: 16 	<ul style="list-style-type: none"> • satisfying DSM-III-R17 criteria for major depression within last 18 months but not in last 2 months, and • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, 		<p>Responders, n NR</p> <p>Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45))</p> <p><i>BDI</i> Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6),</p> <p>Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3)</p> <p>Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7)</p> <p>Change, mean (SD) At week 20 G1: -6.24 G2: -8.44</p> <p>Responders, n NR</p>	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<ul style="list-style-type: none"> • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, • any other primary Axis I disorder at time of index illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions 		<p>Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%) Relapse n(%): At week 20: G1: 18 (23) G2: 10 (13) At week 44 G1: 40 (51) G2: 24 (30) At week 68 G1: 47 (60) G2: 29 (36) Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%; Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93). Over 17 months relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also</p>	

Evidence Table 26. KQ 4. General Tolerability: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>received CT. #2219: Relapse was defined as: (1) meeting DSM-III criteria for major depressive disorder for a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more on HAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms during follow- up phase between 2 successive ratings 2 months apart, reaching a score on HAM-D 17 of at least 13 on both occasions and a level of distress or dysfunction for which the withholding of additional active treatment was no longer justified</p>	

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> McLoughlin et al., 2007⁷ Eranti et al., 2007⁸ Knapp et al., 2008⁹</p> <p><i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital in Invicta Mental Health Trust in Kent, 65.2% were inpatients</p> <p><i>Funding</i> National Health Service Research and Development, National Coordinating Centre for Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating major depressive</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters)</p> <p><i>Type of analysis</i> m-ITT</p> <p><i>N</i> 46</p> <p><i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p>	<p><i>TRD definition</i> • All patients referred for ECT: • No failure required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Right handed patients • more than 18 years old • referred for ECT due to major depressive episode</p> <p><i>Exclusion criteria</i> • Inability to have rTMS because of metallic implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent.</p>	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0)</p> <p><i>Polarity, % MDD</i> G1: 91.67 G2: 90.91</p> <p><i>Bipolar</i> G1: 8.33% G2: 9.09 %</p> <p><i>Age, mean yrs</i> G1: 63.6 G2: 68.3</p> <p><i>Sex, % females</i> G1: 67.7 G2: 72.7</p> <p><i>Right handed, % Overall: 100%</i></p> <p><i>HAM-D 17 Baseline n</i> G1: 22 G2: 24</p> <p><i>Baseline score, mean (SD)</i> G1: 24.8 (5.0) G2: 23.9 (7.0)</p>	<p><i>HAM-D 17 Analyzed n</i> G1: 22 G2: 23</p> <p><i>Endpoint score, mean (SD)</i> End of treatment G1: 10.7 G2: 18.5 <i>P</i> = 0.002, effect size of 1.44</p> <p><i>Follow-up at 6 months</i> G1: NR G2: NR <i>P</i> = 0.93</p> <p><i>Change, mean (SD)</i> End of treatment G1: -14.1 G2: -5.4 <i>P</i> = 0.017</p> <p><i>Responders, n</i> End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p><i>Remitters, n</i> HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22</p> <p><i>Baseline score, mean (SD)</i> G1: 48.9 (12.6) G2: 42.7 (7.5)</p> <p><i>Other:</i> QALYs Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</p> <p>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (p = 0.987). This</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>episodes in patients referred for ECT</p> <p><i>Quality Rating</i> Good</p>	<p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%):110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions:15 <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 		<p><i>BDI</i>: Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD)</p> <p>NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p> <p>Responders, n NR</p> <p>Remitters, n NR</p>	<p>suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>(verbal fluency, anterograde memory, and retrograde memory)</p> <p><i>MMSE</i> Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9)</p> <p>Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)</p> <p>Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3)</p> <p>Change, mean (SD): G1: 1.3 G2: -1.3 <i>P</i> < 0.08</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Attrition</i> Overall to end of treatment 6/46, at 6 months 9/46</p> <p>At end of treatment, % G1: 6/24 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 5/24 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> O'Connor, 2003⁶⁴</p> <p><i>Country, setting</i> United States, University Hospital, inpatient vs. outpatient population not clearly reported</p> <p><i>Funding</i> NIH/NIMH and a NARSAD grant</p> <p><i>Research Objective</i> Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition</p> <p><i>Quality Rating</i> Poor</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 28</p> <p><i>Duration</i> • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt</p> <p><i>Medications allowed</i> rTMS patients completed a washout of all psychotropic medications while ECT continued all medications</p> <p><i>Strategy</i> Switch strategy for rTMS and augment or add-on strategy for ECT group</p> <p><i>Interventions</i> G1: ECT G2:</p>	<p><i>TRD definition</i> • Patients referred for ECT • AD failures not required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Met criteria for MDD • HRSD > 18</p> <p><i>Exclusion criteria</i> • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2</p> <p><i>HAM-D</i> Baseline n Completers G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) <i>P</i> = 0.001</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)</p>	<p>HAM-D Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5)</p> <p>Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time <i>P</i> < 0.01</p> <p>Responders, n G1: NR G2: 0</p> <p>Remitters, n G1: NR G2: 100%</p> <p><i>Other</i> Validated measure Yes</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)</p>	<p><i>Quality of Life</i></p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning)</p> <p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09)</p> <p>Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00)</p> <p>Change, mean (SD) G1: 46.92 (10.80)/ Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: <i>P</i> > 0.05 G2: 44.07 (10.43)</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>ECT</p> <ul style="list-style-type: none"> • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12, <p>rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks 			<p>Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with 2 week follow-up results ($P > 0.05$)</p> <p>No significant interaction between treatment sessions and groups with respect to LN ($P > 0.05$)</p>	<p>RAVLT, Acquisition, mean (SD)</p> <p>Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09).</p> <p>End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) $P < 0.01$.</p> <p>Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) $P > 0.05$.</p> <p>RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD)</p> <p>Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08)</p> <p>End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80)</p> <p>Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07).</p> <p>Transient News Events Test (TNET-measure of retrograde memory)</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12)</p> <p>Endpoint score, mean (SD) G1: 39.10 (13,.21) G2: 57.81 (18.33)</p> <p>Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12)</p> <p>Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$.</p> <p>Cognitive function/memory impairment reported as primary outcome measures.</p> <p>MMSE NR</p>

Evidence Table 27. KQ 4. General Tolerability: Tier 3 (ECT vs. rTMS—MDD) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<i>Attrition</i> Overall, % No attrition At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> NR

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> George et al., 1997³⁵</p> <p><i>Country, setting</i> USA, outpatient setting</p> <p><i>Funding</i> NARSAD, Ted and Vada Stlanley Foundation</p> <p><i>Research Objective</i> To test hypothesis: daily left prefrontal rTMS has antidepressant effects</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT, crossover</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 12</p> <p><i>Duration</i> 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt</p> <p><i>Interventions</i> G1: rTMS G2: sham stimulation</p> <p><i>Medications Allowed</i> ADs tapered for 9, 3 partial responders continued their medication</p> <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20</p>	<p><i>TRD definition</i> • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • DSM-IV criteria for current MDD • right-handed</p> <p><i>Exclusion criteria</i> • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma</p>	<p><i>Treatment Failure</i> Number of previous AD medications Overall: 13.4</p> <p><i>Polarity, %</i> Unipolar Overall: 91.7</p> <p>Bipolar II Overall: 8.3</p> <p><i>Age, mean yrs</i> Overall: 41.8 (12.4)</p> <p><i>Sex, % females</i> Overall: 91.7</p> <p><i>Right handed, %</i> Overall: 100</p> <p><i>HAM-D 21</i> Baseline n G1: 12 G2: 12</p> <p>Baseline score, mean (SD) Overall: 28.5 (4.2)</p>	<p><i>HAM-D 21</i> G1: rTMS G2: sham stimulation</p> <p>Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 P < 0.03</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, % G1: 4/12 G2: NR</p> <p>Suicidality, % G1: 0 G2: Sham: 1/12</p> <p>Seizures: None</p> <p>Unexpected side effects: None</p> <p>Headaches NR by active v. sham</p> <p>Memory or Attention: None</p> <p><i>Attrition</i> Overall: 0</p> <p><i>Adherence/ compliance</i> N</p>

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 2 • Inter-train interval: NR • Pulses per session: 800 • Total number of sessions: 5/wk for a total of 20 per patient <p>Sham:</p> <ul style="list-style-type: none"> • Same as above but angled at 45 degrees from skull 				
<p><i>Author, Year</i> West, 198140</p> <p><i>Country, setting</i> UK, Hospital, inpatient</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> The therapeutic effect of simulated and real bilateral electric convulsion therapy</p> <p><i>Quality Rating</i> KQ1 - Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers or per protocol (PP)</p> <p><i>N</i> 25 (22 analyzed)</p> <p><i>Duration</i> 3 weeks</p> <p><i>Interventions</i> G1: ECT G2: Simulated ECT</p> <p><i>Medications Allowed</i> 50 mg amitriptyline</p> <p><i>Strategy</i> Combination</p>	<p><i>TRD definition</i> • Referred for ECT</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Primary depressive illness</p> <p><i>Exclusion criteria</i> • NR</p>	<p><i>Subgroups</i> NR</p> <p><i>Baseline n</i> G1: 13 G2: 12</p> <p><i>Treatment Failure</i> NR</p> <p><i>Polarity, %</i> NR</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 52.0 G2: 53.3</p> <p><i>Sex, % females</i> G1: 45 G2: 36</p>	<p><i>N Analyzed</i> G1: 11 G2: 11</p> <p><i>BDI</i> Yes G1: ECT G2: Simulated ECT</p> <p>Endpoint score, mean (SD) G1: 10.8 (SEM 2.6) G2: 22.2 (3.8) $P < 0.002$</p> <p>Change, mean (SD) G1: -15.8 G2: -1.9</p> <p>Responders, n NR</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results None reported</p> <p>Predefined NA - No AE data reported</p> <p>Adequate information NA - No AE data reported</p>

Evidence Table 28. KQ 4. General Tolerability: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> The anaesthetic agent was Althesin (alphadolone) and the muscle relaxant suxamethonium. Electric convulsion therapy was administered from a Transycon machine using 40 joules with double-sided unrectified waveform and bilateral anterior temporal placement of the electrodes.</p>		<p><i>Race, % white</i> NR</p> <p><i>Not Specified, %</i> NR</p> <p><i>Right handed, %</i> NR</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 26.6 (SEM 2.8) G2: 24.1 (3.5)</p>	<p>Remitters, n NR</p> <p>Other</p>	<p><i>Attrition</i></p> <p>Overall, % 12%</p> <p>At end of treatment, % G1: 15.4 G2: 8.3</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, % G1: 7.7 G2: 8.3</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other</p> <p><i>Adherence/ compliance</i> None reported</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Rosa et al., 2006²</p> <p><i>Country, setting</i> Brazil, university clinic, inpatients and outpatients included</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To Compare efficacy and side effects associated with rTMS and ECT in an adult population with TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Included completers analysis & ITT (LOCF), ITT is reported in abstraction</p> <p><i>N</i> 42</p> <p><i>Duration</i> Active txt 2-4wks (rTMS pts not responding after 2 wks switched over to ECT), Primary Outcome: HAM-D response at 4wk</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medications allowed</i> ADs, antipsychotics, mood stabilizers were discontinued while anti-anxiety meds were allowed/initiated as needed</p> <p><i>Strategy</i> Switch</p>	<p><i>TRD definition</i> • A lack of response to at 2+ antidepressants of different classes used for at least 4 wk with adequate dosages, with augmentation (with lithium or thyroid hormone for at least 1 trial) • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Age 18-65 • unipolar depressive disorder (Ham-D >=22) w/o psychotic symptoms</p> <p><i>Exclusion criteria</i> • History of epilepsy, neurosurgery with presence of metal clips, other neurological or psychiatric disease • Use of cardiac pacemaker • Pregnancy</p>	<p><i>Treatment Failure</i> Previous treatment, not specified, % Overall: 100%</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 46.0 G2: 41.8</p> <p><i>Sex, % females</i> G1: 46.7 G2: 60.0</p> <p><i>Race, % white</i> G1: 80.0 G2: 90.0</p> <p><i>HAM-D 17</i> Baseline n G1: 20 G2: 22</p> <p>Baseline score, mean (SD) G1: 32.1 (5.0) [based on completers N = 15] G2: 30.1 (4.7) [N = 20]</p> <p><i>CGI</i> Baseline n G1: 20 (N analyzed =15)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) NR (graph only)</p> <p>Change, mean (SD) NR (graph only) P = 0.86</p> <p>Responders, n (%) G1: 6 (20) G2: 10 (45) P = 0.35</p> <p>Remitters, n (%) Ham-D17 <= 7 G1: 3 (15) G2: 2 (9) P = 0.65</p> <p>Instrument CGI Endpoint score, mean (SD) 2wk G1: 4.0 (1.0) G2: 3.7 (1.1) 4wk G1: 3.2 (1.5) G2: 3.1 (1.3)</p> <p>Change, mean (SD) NR, P = 0.672</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Suicidality, % G1: 10.0 G2: 9.1 rTMS: 2 pts developed new psychological symptoms (i.e. 1 = dissociative state, 1 = hypomanic symptoms) and were removed from study</p> <p><i>Neuropsychological or executive functioning</i> NS differences between groups on all neuropsychological tests following wk2 & wk4. (Wechsler Adult Intelligence Scale - R subtests (Vocabulary, Cube), Wechsler Memory Scale subtest (Digit Span), Rivermead Behavioral Memory Test)</p> <p><i>MMSE</i> NR</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> rTMS:</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 25 • Length of train (seconds): 10 • Inter-train interval: 20 • Pulses per session: 2500 • Total number of sessions: 20 over 4 wks <p><i>ECT:</i></p> <ul style="list-style-type: none"> • % receiving bilateral: NR • Intensity: 4.5 times threshold • Number of sessions (range, mean, SD): 10 (1.5) 		<p>G2: 22 (N analyzed =20)</p> <p>Baseline score, mean (SD) G1: 4.7 (0.8) G2: 4.3 (0.8)</p>		<p><i>Other</i></p> <p><i>Attrition</i> Overall, % 16.7</p> <p>At end of treatment, % G1: 15.0* G2: 9.1*</p> <p>*Prior to completing txt (txt end date differed by pt)</p> <p>At end of follow-up, % G1: 25.0 G2: 9.1</p> <p>Withdrawals due to efficacy, % G1: NR G2: 0.0</p> <p>Withdrawals due to adverse events, % G1: NR G2: 9.1</p> <p>Other For ECT, 3 were removed by their treating clinician w/o explanation or evaluation of efficacy</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Schulze-Rauschenbach et al., 2005⁶³</p> <p><i>Country, setting</i> Germany, Psychiatric University Hospital, inpatients</p> <p><i>Funding</i> NR</p> <p><i>Research Objective</i> To compare neurocognitive effects of unilateral ECT and rTMS using a control</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Observational study of patients completing txt</p> <p><i>N</i> 30</p> <p><i>Duration</i> Not clear- testing took place 8.8 days on average afterlast treatment Estimated duration from mean number of txt – ECT 5 weeks and rTMS 3-5 weeks.</p> <p><i>Interventions</i> Control G1: ECT G2: rTMS</p> <p><i>Medications Allowed</i> Antidepressants, low-potency neuroleptics and non-benzodiazepine hypnotics were allowed in both groups. No med changes allowed during study</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Unsuccessful treatment response to at least two different types of antidepressants, each given in a sufficient dosage range for at least 4 weeks Not required or not specified to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Consecutively admitted patients with DSM–IV diagnosis of MDD Age over 18 years <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Previous treatment with ECT or rTMS Additional Axis I diagnosis 	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 46.7 G2: 47.7</p> <p><i>Sex, % females</i> G1: 50 G2: 44</p> <p><i>HAM-D 17</i> Baseline n G1: 14 G2: 16</p> <p>Baseline score, mean (SD) G1: 22.4 (3.1) G2: 21.3 (3.5)</p> <p><i>BDI</i> Baseline n G1: 14 G2: 16</p> <p><i>SSMQ</i> Baseline n G1: 14 G2: 16</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 14.5 (5.7) G2: 13.0 (4.9) Change, mean (SD) G1: -7.9 G2: -8.3 Group x time, <i>P</i> = NS</p> <p>Responders, n G1: 6 (46%) G2: 7 (44%) <i>P</i> = 0.90</p> <p><i>BDI</i> Change, mean (SD) G1: 7.6 G2: 6.4 Group x time, <i>P</i> = NS</p> <p><i>SSMQ</i> Endpoint score, mean (SD) G1: -15.2 (25.2) G2: 3.8 (11.8)</p> <p>Change, mean (SD) G1: 5.5 G2: 20.6</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> One patient in ECT group withdrew due to severe orientation and memory problems following two treatments; data not included.</p> <p><i>Neuropsychological or executive functioning</i> Test scores ECT Pre / Post vs. rTMS Pre / Post Post; <i>P</i> = Post Ect vs. Post rTMS</p> <p>Learning and anterograde memory AVLT Immediate recall (trials 1-5); <i>P</i> = NS Recall after interference (trial 5 minus trial 6) 2.8 (2.2) / 3.9 (1.9) vs. 3.2 (1.9) / 1.8 (2.0); <i>P</i> < 0.01 Recall after delay (trial 5 minus trial 7) 2.4 (1.8) / 4.2 (1.6) vs. 3.2 (1.6) / 2.4 (2.0); <i>P</i> < 0.05 Recognition hits; <i>P</i> = NS and Recognition false alarms; <i>P</i> = NS MPT</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 0 • Intensity: 2.0-2.5 times seizure threshold • Number of sessions (range, mean, SD): 9.9 (2.7) <p>rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 20-30 • Length of train (seconds): 2 • Inter-train interval: 5 • Pulses per session: • Total number of sessions: 2-3/wk <p><i>Strategy</i></p> <p>Augment or add-on</p>		<p>Baseline score, mean (SD)</p> <p>G1: -20.7 (19.0)</p> <p>G2: -16.8 (16.9)</p>		<p>Recall trial; <i>P</i> = NS and Delayed recall; <i>P</i> = NS</p> <p>Retrograde memory Retrograde AVLT Recall; <i>P</i> = NS and Recognition hits; <i>P</i> = NS</p> <p>Recognition false alarms 5.0 (3.0) vs. 1.1 (1.1); <i>P</i> < 0.05</p> <p>Four-card task Free recall 2.0 (1.4) / 0.4 (0.5) vs. 1.4 / (1.2); <i>P</i> < 0.05</p> <p>Recognition; <i>P</i> = NS AMI Recall score; <i>P</i> = NS</p> <p>Subjective memory SSMQ -20.7 (19.0) / -15.2 (25.2) vs. -16.8 (16.9) / 3.8 (11.8); <i>P</i> < 0.05</p> <p>Other cognitive functions MMSE; <i>P</i> = NS, TrailMakingTest A; <i>P</i> = NS, TrailMakingTest B; <i>P</i> = NS, Digit span (WAIS-R); <i>P</i> = NS, Letter-number span; <i>P</i> = NS, Word fluency (LPS); <i>P</i> = NS</p> <p><i>MMSE</i> G1: ECT</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>G2: rTMS G3: Control</p> <p>Baseline n G1: 14 G2: 16 G3: 15</p> <p>Baseline score, mean (SD) G1: 27.9 (1.7) G2: 26.9 (3.4) G3: 29.1 (1.0)</p> <p>Endpoint score, mean (SD) G1: 28.3 (1.3) G2: 27.9 (3.0) G3: 29.2 (1.1)</p> <p>Change, mean (SD) G1: 0.4 G2: -1 G3: 0.01</p> <p>Other P = NS</p> <p><i>Attrition</i> Overall, % 3.3</p> <p>At end of treatment, % G1: 7 G2: 0</p>

Evidence Table 29. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>At end of follow-up, % G1: NR G2: NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 0</p> <p>Withdrawals due to adverse events, % G1: 7 G2: 0</p> <p>One person in ECT group withdrew because of severe orientation and memory problems after 2 ECT treatments; these data were not included in analysis</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Grunhaus et al., 2000⁶²</p> <p><i>Country, setting</i> Israel Sheba Medical Center, inpatients and outpatients</p> <p><i>Funding</i> Established Investigator Award of NARSTAD</p> <p><i>Research Objective</i> To compare rTMS to ECT and psychotic vs. non-psychotic</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 40</p> <p><i>Duration</i> Varied – ECT patients treated for average of 5 weeks, and rTMS pts treated for 4 weeks. Primary outcome measured at end of treatment</p> <p><i>Interventions</i> Overall G1: ECT G2: rTMS</p> <p>Pts with psychosis G3: ECT: G4: rTMS</p> <p>Pts without psychosis G5: ECT G6: rTMS</p> <p><i>Medications allowed</i> • ECT allowed benzodiazepines, neuroleptics antidepressants and</p>	<p><i>TRD definition</i> • Pts referred for ECT: • Only some patients treatment resistant (not defined). Treatment failure not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • age over 18 • DSM-IV diagnosis of MDD • HAM-D17 ≥18 • no personal or first-degree relative history of seizure • no medical, neurological, or neurosurgical disorder that would preclude administration of ECT or rTMS.</p> <p><i>Exclusion criteria</i> • Additional Axis-1 diagnoses</p>	<p><i>Subgroups</i> Patients with and with out Psychosis</p> <p><i>Treatment Failure</i> Failed ≤1 trial, % G1: 50 G2: 25</p> <p>Failed ≥2 trials, % G1: 50 G2: 75</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 63.6 (15.0) G2: 58.4 (15.7)</p> <p><i>Sex, % females</i> G1: 70 G2: 60</p> <p><i>HAM-D 17</i> Baseline n Overall G1: 20 G2: 20 Patients with Psychosis G3: 10 G4: 9 <i>Patients without</i> Psychosis G5: 10 G6: 11</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) At week 2 G1: 17.6 (7.4) G2: 19.3 (8.6) G3: 15.5 (7.6) G4: 23.4 (5.5) G5: 19.7 (7.0) G6: 15.8 (9.3)</p> <p>End of treatment G1: 11.2 (8.4) G2: 15.4 (7.5) G3: 8.4 (5.3) G4: 20.8 (5.0) G5: 13.9 (10.3) G6: 11.0 (6.2)</p> <p>Change, mean (SD) At week 2 G1: 10.8 G2: 6.5 G3: 16.0 G4: 5.3 G5: 5.5 G6: 7.7</p> <p>End of treatment G1: 17.2 G2: 10.4 Group x time, <i>P</i> = 0.09 G3: 23.1 G4: 7.9 Group x time, <i>P</i> = 0.005 G5: 11.3</p>	<p><i>Quality of Life</i></p> <p>Scale Pittsburg Sleep Quality Index</p> <p>Intervention G1: ECT G2: rTMs G3: NR G4: ECT Psychotic vs none G5: rTMS Psychotic vs none</p> <p>Baseline n G1: 20 G2: 20 G3: NR G4: 10 vs. 10 G5: 9 vs. 11</p> <p>Baseline score, mean (SD) G1: 12.5 (4.4) G2: 11.7 (5.7) G3: NR G4: 12.1 (5.5) vs 12.9 (3.1) G5: 14.1 (4.9) vs 9.7 (5.8)</p> <p>Endpoint score, mean (SD) G1: Awk2 8.8 (4.5) / endpoint 6.8 (3.5)</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>anticonvulsants in stable doses</p> <ul style="list-style-type: none"> rTMS All psychiatric medications were discontinued only clonazepam (1–2 mg/day, given in twice-daily doses) was started in all patients to decrease anxiety, provide relief of severe insomnia, and have an additional protective element regarding seizures <p><i>Strategy</i> Mixed-between group differences</p> <p><i>Parameters</i> ECT: <ul style="list-style-type: none"> % receiving bilateral: 40 switched after non-response Intensity 2.5-fold seizure threshold Number of sessions - mean 9.6 sessions (range 7-14) </p> <p>rTMS <ul style="list-style-type: none"> Frequency (Hz):10 Motor threshold (%):90 Number of trains:NR </p>		<p>Baseline score, mean (SD)</p> <p>G1: 28.4 (9.3) G2: 25.8 (6.1) G3: 31.5 (11.5) G4: 28.7 (5.6) G5: 25.2 (5.3) G6: 23.5 (5.6)</p>	<p>G6: 12.5 Group x time, $P = NS$</p> <p>Responders if the final HRSD had decreased to 50% or more from baseline and the final GAS < 60.</p> <p>Responders, n End of txt G1: 16 (80%) G2: 9 (45%) G3: 10 (100%) G4: 2 (22%) $P \leq 0.01$ G5: 6 (60%) G6: 7 (63%) $P = NS$</p>	<p>G2: Awk2 10.1 (3.7) / endpoint 10.5 (3.9) G3: NR G4: Awk2 8.0 (4.5) / endpoint 5.8 (2.1) vs G5: Awk2 12.2 (2.8) / endpoint 12.3 (3.6) vs. Awk2 8.4 (3.5) / endpoint 9.1 (3.8)</p> <p>Change, mean (SD) G1: Awk2 3.7 / endpoint 5.7 G2: Awk2 1.6 / endpoint 1.2 G3: G4: Awk2 4.1 / endpoint 6.3 vs Awk2 4.9 / endpoint 7.1 G5: Awk2 11.9 / endpoint 1.8 vs. Awk2 1.3 / endpoint 0.6</p> <p>Other Overall Group F 1.8 (df 1,36) $P = NS$ Time F 12.5 (df 2,72) $P = 0.000$ Interaction F 4.6 (df 2,2) $P = 0.010$ Non-psychotic Group F 0.5 (df 1,18) $P = NS$</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> •Length of train (seconds):2 or 6 • Inter-train interval:NR • Pulses per session: 400 or 1200 • Total number of sessions: 20 				<p>Time F 4.4 (df 2,36) $P = 0.020$ Interaction F 2.3 (df 2,2) $P = NS$ Psychotic Group F 9.8 (df 1,16) $P = 0.006$</p> <p><i>Quality of Life</i> Overall Group F 1.8 (df 1,36) $P = NS$ Time F 12.5 (df 2,72) $P = 0.000$ Interaction F 4.6 (df 2,2) $P = 0.010$ Non-psychotic Group F 0.5 (df 1,18) $P = NS$ Time F 4.4 (df 2,36) $P = 0.020$ Interaction F 2.3 (df 2,2) $P = NS$ Psychotic Group F 9.8 (df 1,16) $P = 0.006$</p> <p>Scale Global Assessment of Function Scale</p> <p>Intervention G1: ECT G2: rTMS G3:</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>G4: ECT Psychotic vs none G5: rTMS Psychotic vs none</p> <p>Baseline n G1: 20 G2: 20 G3: G4: 10 vs. 10 G5: 9 vs. 11</p> <p>Baseline score, mean (SD) G1: 31.0 (8.5) G2: 34.1 (11.7) G3: Intervention4: 29.0 (7.0) vs. 33.0 (9.8) G5: 28.9 (9.9) vs. 38.3 (11.8)</p> <p>Endpoint score, mean (SD) G1: Awk2 46.8 (17.2)/ endpoint 61.5 (21.5) G2: Awk2 44.5 (14.7)/ endpoint 51.0 (18.2) G3: G4: Awk2 50.6 (18.3)/ endpoint 65.5 (18.8) vs. Awk2 43.0 (16.0)/ endpoint 57.5 (24.2) G5: Awk2 36.1 (8.2)/ endpoint 39.4 (14.5.) vs. Awk2 51.4 (15.5)/ endpoint 60.5</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Change, mean (SD) G1: Awk2 15.8 / endpoint 30.5 G2: Awk2 10.4 / endpoint 16.9 G3: G4: Awk2 21.6 / endpoint 36.5 vs. Awk2 10.0 / endpoint 24.5 G5: Awk2 7.2 / endpoint 10.5 vs. Awk2 13.1 / endpoint 22.2</p> <p>Other Overall Group F 0.7 (df 1,38) <i>P</i> = NS Time F 40.8 (df 2,76) <i>P</i> = 0.000 Interaction F 3.4 (df 2,2) <i>P</i> = 0.040 Non-psychotic Group F 1.0 (df 1,19) <i>P</i> = NS Time F 19.8 (df 2,38) <i>P</i> = 0.000 Interaction F 0.3 (df 2,2) <i>P</i> = NS Psychotic Group F 8.2 (df 1,17) <i>P</i> = 0.01</p> <p><i>Adverse Events</i> NR 5 rTMS patients had mild headaches</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Neuropsychological or executive functioning Measures, Results</i> MMS. (ECT baseline 25.9 (4.1), ECT end of treatment 24.5 (7.6); rTMS baseline 24.8 (4.1), rTMS end of treatment 26.3 (3.9), repeated measures ANOVA [group effect $F(1,29) = 0.1, P = NS$; time effect $F(2,58) = 1.3, P = NS$; interaction $F(2,2) = 2.3, P = NS$) analysis was also performed for psychotic–non-psychotic groups with similar results.</p> <p>Predefined No</p> <p><i>MMSE</i></p> <p>Baseline n G1: 20 G2: 20</p> <p>Baseline score, mean (SD) G1: 25.9 (4.1) G2: 24.8 (4.1)</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Endpoint score, mean (SD) G1: 24.5 (7.6) G2: 26.3 (3.9)</p> <p>Change, mean (SD) G1: -1.4 G2: +1.5</p> <p>Other ANOVA [group effect $F(1,29) = 0.1, P = NS$; time effect $F(2,58) = 1.3, P = NS$; interaction $F(2,2) = 2.3, P = NS$) analysis was also performed for psychotic–nonpsychotic groups with similar results.</p> <p><i>Adequate information</i></p> <p><i>Attrition</i> Overall, % 0%</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % 0</p> <p>Withdrawals due to efficacy, % 0</p>

Evidence Table 30. KQ 4. Adherence: Tier 1 (ECT vs . rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> Compliance All patients completed study

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Garcia-Toro et al., 2006¹⁷</p> <p><i>Country, setting</i> Spain, single center, all outpatients</p> <p><i>Funding</i> Fundacio La Marato de TV3</p> <p><i>Research Objective</i> To assess the efficacy of high and low frequency rTMS and different locations of activation</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in analysis</p> <p><i>N</i> 30</p> <p><i>Duration</i> • Primary outcome after 2 weeks of active treatment • Follow-up: 2 weeks post treatment</p> <p><i>Interventions</i> G1: Sham G2: rTMS G3: rTMS + SPECT (focused on different regions of brain after examination with single photon emission computed tomography [SPECT] exam)</p> <p><i>Medications allowed</i> All pts continued (failed) AD medication and other psychotropic meds</p> <p><i>Strategy</i> Augmentation</p>	<p><i>TRD definition</i> • Failed 2+ txt trials at 4+ weeks • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • At least 18 yrs old, MDD, unipolar</p> <p><i>Exclusion criteria</i> • Contraindications for rTMS and high suicide risk</p>	<p><i>Subgroups</i> None</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100%</p> <p><i>Age, mean yrs</i> G1: 47.2 G2: 48.5 G3: 51.1</p> <p><i>Sex, % females</i> G1: 70 G2: 40 G3: 40</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> G1: 90% G2: 100% G3: 100%</p> <p><i>HAM-D 21</i> Baseline n G1: 10 G2: 10 G3: 10</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) At week 1 G1: 23.6 (7.04) G2: 24.1 (7.91) G3: 21.6 (3.10)</p> <p>At week 2 G1: 23.6 (7.79) G2: 20.10 (8.18) G3: 18.10 (6.15)</p> <p>Follow-up 2 weeks post treatment G1: 23.67 (5.55) G2: 20.88 (7.26) G3: 16.9 (7.0)</p> <p>Change, mean (% change) At 1 week G1: -1.5 (-5.9%) G2: -3.2 (-13.27%) G3: -3.4 (-13.6%)</p> <p>At 2 weeks G1: -1.5 (-5.9%) G2: -7.2 (-26.37%) G3: -6.9 (-27.6%) G1: vs. G2+G3 (mean = 7.05), <i>P</i> = 0.048</p> <p>Follow-up at week 4 G1: -1.43 (-5.6%) G2: -6.42 (-23.51%) G3: -8.1 (-32.4%)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % at 2 weeks 0%, during two week follow-up 3 patents withdrew due to changes in pharmacotherapy</p> <p>At end of treatment, % G1: 0 G2: 0 G3: 0</p> <p>At end of follow-up, % NR</p> <p>Does not report which group 3 patients came from</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>rTMS+SPECT received active rTMS that was focused on different regions of brain after examination with single photon emission</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>rTMS Low:</p> <ul style="list-style-type: none"> • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 60 • Inter-train interval: • Pulses per session: 1800 • Total number of sessions: 10 in 2 wks <p>High</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 110 • Number of trains: 30 • Length of train (seconds): 2 • Inter-train interval: 20+5 • Pulses per session: 1200 • Total number of sessions: 10 in 2 wks <p>Sham</p> <ul style="list-style-type: none"> • Same but with coil angling 45 degrees away from scalp 		<p>Baseline score, mean (SD)</p> <p>G1: 25.10 (7.28) G2: 27.30 (4.97) G3: 25.00 (4.14)</p> <p><i>CGI-S</i></p> <p>Baseline n</p> <p>G1: 10 G2: 10 G3: 10</p> <p>Baseline score, mean (SD)</p> <p>G1: 4.7 (0.82) G2: 4.8 (1.0) G3: 4.8 (0.63)</p>	<p>G1: vs. G2+G3, $P = 0.121$</p> <p>Responders, n (%)</p> <p>G1: 0 (0) G2: 2 (20) G3: 2 (20)</p> <p>$P = NR$</p> <p><i>CGI-S</i></p> <p>Endpoint score, mean (SD)</p> <p>At 2 weeks</p> <p>G1: 4.6 (0.97) G2: 3.8 (1.48) G3: 3.9 (0.99)</p> <p>2 week follow-up</p> <p>G1: 4.75 (1.16) G2: 4.00 (1.15) G3: 3.7 (1.57)</p>	<p>computed tomography (20-Hz rTMS to an area of relatively low activity and 1-Hz rTMS to an area showing relatively high activate</p> <p><i>Adherence/ compliance</i></p> <p>Compliance</p> <p>all patients completed active 2 week treatment</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Avery et al., 2006¹⁰</p> <p><i>Country, setting</i> USA, Single center, University department of psychiatry, outpatient</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To test hypothesis that patients receiving active TMS would show a greater antidepressant response rate than those receiving sham stimulation</p> <p><i>Quality Rating</i> Good Fair for KQ2 and subgroups¹¹ (small number of people followed for relapse; used a single measure and did not account for additional medical conditions)</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 68</p> <p><i>Duration</i> 4 weeks (15 sessions) of txt, primary assessment 1 week after completion of txts. Responders were evaluated for relapse 2 wks after primary endpoint</p> <p><i>Interventions</i> G1: High-left TMS G2: Sham</p> <p><i>Medications Allowed</i> • Pts encouraged, although not required, to discontinue current antidepressant medication, sedatives, or benzodiazepines; (continuing AD medication G1: 31% vs. G2: 27%; continuing benzodiazepines G1: 26% vs. G2: 24%)</p>	<p><i>TRD definition</i> • Failed to respond to or unable to tolerate at least 2+ adequate AD trials (defined by score ≥ 3 on ATHF) • Failures not required to be in current episode <i>Tier 1</i></p> <p><i>Inclusion criteria</i> • TRD • 21 to 65 years old • DSM-IV criteria for current major depressive disorder (MDD) • HAM-D 17 ≥ 17 and a decrease of no more than 20% between screening and 1st txt day</p> <p><i>Exclusion criteria</i> • Previous TMS exposure • bipolar disorder, • previous failure of nine or more bitemporal ECT treatments • current major depressive episode longer than 5 years • history of substance abuse or dependence with in past 2 years, • antisocial or borderline personality disorder,</p>	<p><i>Subgroups</i> Pain, subgroup analysis presented in Avery et al, 2007¹¹</p> <p>Baseline n G1: 35 G2: 33</p> <p><i>Treatment Failure</i></p> <p>Current episode failures, mean (SD) G1: 1.46 (0.78) G2: 1.48 (0.67)</p> <p>Mean failed trials (SD) G1: 3.2 (2.44) G2: 3.3 (1.72)</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 44.3 G2: 44.2</p> <p><i>Sex, % females</i> G1: 60 G2: 52</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> NR</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 15.7 G2: 19.8</p> <p>Change, mean (SD) G1: -7.8 (7.8) G2: -3.7 (6.3) Group x time $P = 0.002$</p> <p>Responders, n G1: 11 (31.4%) G2: 2 (6.1%) $P = 0.008$</p> <p>Remitters, n HAM-D21 < 10 G1: 7 (20.0%) G2: 1 (3.0%) $P = 0.033$</p> <p>No Relapse (at 6mos), N G1: 5 G2: Unknown (1 relapsed, 1 loss to follow after 3 mos of without relapse)</p> <p><i>BDI</i> Change, mean (SD) G1: 11.3 (12.8) G2: 4.8 (8.5) Random Regression analyses revealed significant group by time interaction ($P = 0.003$)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR Site pain first session sham none (0/33) vs. TMS group, 41% (14/35) 15th session sham 3% (1/30) vs. TMS 33% (11/33). The discomfort pain scale ratings (0-4) decreased in TMS group in subsequent treatment sessions, decreasing from a mean of 1.89 (1.02) at session 1 to 1.11 (1.03) at session 15 ($t = 4.24, P < 0.001$).</p> <p>Changes from baseline in 128 individual SAFTEE scores - emerging symptoms were analyzed by chi-square analyses at visits 5, 10, 15, and 16 with a Bonferroni correction, there were no significant differences between TMS and sham in any of emerging symptoms. (Data = NR)</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Those stopping medications had to be medication-free for at least 2 weeks All responders given AD post rTMS treatment (active or sham) <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> Frequency (Hz):10 Motor threshold (%): 110 Number of trains: 32 Length of train (seconds): 5 Inter-train interval: 25-30 Pulses per session: 1600 Total number of sessions: 15 in 4 wks <p>Sham</p> <ul style="list-style-type: none"> Identical stimulation parameters Lateral edge of coil rotated 90° away from scalp 	<ul style="list-style-type: none"> active suicidal ideation current symptoms of psychosis, Hx of seizure disorder, Hx of closed head injury with loss of consciousness or prior brain surgery any other major psychiatric or medical comorbidity 	<p>Groups similar at baseline Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 23.5 (3.9) G2: 23.5 (2.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 28.1 (8.7) G2: 28.4 (8.0)</p>		<p><i>Neuropsychological or executive functioning</i> No sig differences in GOAT, RAVLT, WAIS-R, COWAT, and SAFTEE; SUBGROUP ANALYSIS¹¹: At 15th session pain TMS 33% vs, sham 3% ($P < 0.05$) no statistically significant ($P > 0.05$) time by treatment group interactions for any of neuropsychological test measures. models were refit without interaction term, there was no significant treatment group main effect ($P > 0.05$) evident for any of neuropsychological tests, indicating groups had similar levels of neuropsychological performance collapsed over time. Several measures showed significant main effects of time, that is, collapsed over groups, there was significant</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>improvement in individual neuropsychological test performances for both groups.</p> <p>No confusion was associated with TMS treatments. GOAT assessments were well within normal range and ranged from 98 to 100. No significant ($P > 0.05$) differences between groups for any session.</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % 7.4% (5/68)</p> <p>At end of treatment, % NR At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 0 G2: 3.0</p> <p>Withdrawals due to adverse events, % G1: 0 G2: NR</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Very unclear as to when patients discontinued <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Bretlau, 2008⁴¹</p> <p><i>Country, setting</i> Denmark, setting NR, outpatients</p> <p><i>Funding</i> Commercial source—please list name.supported by Medicin Valley Academy and an unrestricted research grant from H Lundbeck A/S</p> <p><i>Research Objective</i> To do an interim analysis of a study on active rTMS combined with escitalopram versus sham TMS combined with escitalopram in the acute treatment</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 49</p> <p><i>Duration</i> 12 weeks, but primary outcome was at 3 weeks after 15 rTMS sessions completed over a three week period. Escitalopram was administered during the entire trial at 20mg daily (10 mg daily for first wk of trial). Primary outcome (HAM-D6) was recorded at baseline, wk 2, 2k 3, 2k 5, 2k 8, and wk 12. Secondary outcome measures (HAM-D17 and MES) were recorded at the same intervals.</p>	<p><i>TRD definition Required to be in current episode</i> Yes</p> <p><i>Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i> Aged 18 - 75 years; meet DSM-IV criteria for current major depressive disorder but not chronic subtype (i.e. current episode not > 24 months); failed to respond to at least one previous adequate (at least 6 weeks) antidepressant treatment during the current episode; subjects with heart disorders or diabetes were included if they were in a somatically stable phase</p>	<p><i>Subgroups</i> No sub-group analysis</p> <p>Treatment Failure Failed 1 or more, % G1: 100 G2: 100</p> <p>Failed 2 or more, % G1: NR G2: NR</p> <p>Current episode failures, mean G1: 2.8 (0.9) G2: 2.5 (0.9)</p> <p>Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: NR G2: NR Bipolar I G1: NR G2: NR</p>	<p><i>HAM-D</i> Yes HAM-D 17 Other, please describe.HAM-D 6 G1: rTMS + escitalopram G2: sham TMS + escitalopram</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p> <p>Baseline score, mean (SD) G1: HAM-D 17 = 25.3 (3.0); HAM D 6 = 14.0 (1.0) G2: HAM-D 17 = 24.7 (3.2); HAM D 6 = 13.3 (1.5)</p> <p>Endpoint score, mean (SD) G1: HAM-D 17: Awk2 = 19.8 (5.1), Awk3 = 16.4 (4.5), FU wk 5 = 14.5 (5.2), FU</p>	<p><i>Quality of Life</i> NR</p> <p>Adverse Events Overall NR</p> <p>Amnesia, % G1: memory impairment: 3wk/ 12 wk mean: 0.00/0.00 G2: 0.13/0.00</p> <p>Cardiovascular adverse events, % G1: palpitations: 3wk/ 12 wk mean: 0.23/0.14 G2: 0.30/0.12</p> <p>Cognitive impairment, % G1: concentration difficulties 3wk/ 12 wk mean: 1.43/0.71 G2: 1.52/1.22</p> <p>Headache, % G1: 3wk/ 12 wk mean: 0.18/0.10 G2: 0.43/0.06</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Interventions</i> B - Repetitive Transcranial Magnetic Stimulation (rTMS)E - Placebo G1: rTMS + escitalopram (n = 25) G2: sham TMS + escitalopram (n = 24) G1: rTMS + escitalopram G2: sham TMS + escitalopram G1: rTMS + escitalopram** G2: sham TMS + escitalopram**</p> <p><i>Parameters</i> Location = Left Dorsolateral prefrontal cortex Frequency = 8 Hz Intensity = 90% motor threshold Per session = 20 trains of 8 seconds at 52-second intervals. Each txt session lasted 20 minutes. Number of sessions = 15</p>	<p><i>Exclusion criteria</i> Concurrent diagnosis of an organic brain disorder such as mental retardation, schizophrenia, or other psychotic disorders or personality disorders; potential risk factors for escitalopram such as hypersensitivity to the Intervention, intake of monoamine-oxidase inhibitors of the irreversible type with the past 14 days, pregnancy or insufficient contraception in females of reproductive age; risk factors for TMS such as history of epilepsy, metal implants in the head or neck regions, pacemaker or other electronic implants, receiving antipsychotics; having major suicide ideation.</p>	<p>Bipolar II G1: NR G2: NR</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 53.1 G2: 57.8</p> <p><i>Sex, % females</i> G1: 68% G2: 57%</p> <p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Not Specified, %</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR</p> <p>Groups similar at baseline Yes</p> <p><i>Tier</i> Tier 22A: 1+ failed, MDD</p>	<p>wk8 = 12.4 (5.8), FU wk12 = 11.1 (6.7); HAM D 6 = Awk2 = 11.5 (2.6), Awk 3 = 10.0 (2.5), FU wk 5 = 8.9 (2.6), FU wk 8 = 7.9(3.1), FU wk 12 6.7 (4.1) G2: HAM-D 17: = A wk 2 = 22.3(4.5), A wk 3 = 19.1 (4.8), FU wk 5 = 16.3 (5.1), FU wk 8 = 15.3 (6.4), FU wk 12 = 13.5 (7.2); HAM D 6: Awk 2 = 12.5(2.3), A wk 3 = 11.4 (2.7), FU wk 5 = 10.0 (2.9), FU wk 8 = 8.9 (3.6) FU wk 12 = 8.1 (4.2)</p> <p>Change, mean (SD) G1: HAM-D 17 = 14.2 ; HAM D 6 = 7.3 G2: HAM-D 17 = 11.2; HAM D 6 = 5.2</p> <p>Responders, n G1: NR G2: NR</p> <p>Remitters, n G1: NR G2: NR</p>	<p>Insomnia, % G1: reduced duration of sleep 3wk/ 12 wk mean: 0.45/0.24 G2: 0.91/0.39</p> <p>Somnolence, % NR Suicidality, % NR</p> <p>Additional Comments **Adverse events are reported by the UKU side-effect scale and reported as mean and standard deviation** Sig differences (P <= 0.05) compared to active: at 3wks, with sham pts have higher reduction in sleep; at 12 wks, more sham pts have concentration difficulties Study utilized the UKU scale as listed before - Other adverse events include: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63);</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Strategy</i> Augment or add-on strategy, for example the patients current treatment of an SSRI was added to or augmented with another treatment</p>			<p><i>Other</i> The effect size on the primary outcome measure (HAM-D 6) was greatest after two weeks of therapy (0.80 in favour of rTMS), but after 3 weeks of therapy, the effect size was 0.65 (still > 0.40). It remained above 0.40 at the 12 week endpoint (0.47). HAM-D17 Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.83 (0.22-1.44), P = 0.02; HAM-D17 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.78 (0.18 - 1.39), P = 0.01; HAM-D17 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.48(-0.12 - 1.07), P = 0.09; HAM-D17 FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.64 (0.04 - 1.24),</p>	<p>Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12=0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk 12 =0.94 (0.73); rTMS A wk 3 = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36);</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>P = 0.05; HAM-D17 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.47 (-0.11 - 1.07), P = 0.22;</p> <p>HAM-D6 Awk 2 Effect size (95% CI) and Mann-Whitney P: 0.73 (.018 -1.39), P = 0.05; HAM-D6 Awk 3 Effect size (95% CI) and Mann-Whitney P: 0.80 (0.20 - 1.42), P = 0.01; HAM-D6 FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.65 (0.09 -1.29), P = 0.02; HAM-D6 FU wk 8 Effect size (95% CI) and Mann-Whitney P:0.50 (-0.10 - 1.09), P = 0.10; HAM-D6 FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.0.50 (-0.10 - 1.09), P = 0.09;</p>	<p>Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p>Neuropsychological or executive functioning No</p> <p>Measures, Results NR</p> <p>Predefined Yes</p> <p>MMSE No NR</p> <p>Baseline n NR</p> <p>Baseline score, mean (SD) NR</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) NR</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p><i>BDI</i> G1: rTMS + escitalopram* (See comments) G2: sham TMS + escitalopram</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p> <p>Baseline score, mean (SD) G1: 23.9 (2.4) G2: 23.0 (3.0)</p> <p>Endpoint score, mean (SD) G1: A wk 2 = 19.5 (4.4), A wk 3 = 16.5 (4.7), FU wk 5 = 14.2 (4.7), FU wk 8 = 12.8, FU wk 12 = 11.5 (6.8) G2: A wk 2 = 21.3 (4.1), A wk 3 = 19.2 (4.4), FU wk 5 = 16.4 (5.2), FU wk 8 = 15.4 (6.2), FU wk 12 = 13.6 (6.9)</p> <p>Change, mean (SD) G1: 12.4 G2: 9.4</p>	<p>Other Yes Study utilized the UKU scale as listed before - Other adverse events include: tension/inner unrest: Sham AK wk 3 = 1.48 (0.67)/ FU wk 12 = 0.89 (0.32); rTMS A wk 3 = 1.36 (0.49), FU wk 12 1.00 (0.63); Tremor: Sham AK wk 3 = 0.17 (0.39)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.12); Akathisia: Sham AK wk 3 = 0.04 (0.21)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.21), FU wk 12 0.00 (0.00); Nausea: Sham AK wk 3 = 0.35 (0.49)/ FU wk 12 = 0.17 (0.51); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.05 (0.22); Diarrhea: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.14 (0.35), FU wk 12 0.10 (0.30); Diminished Sexual Desire: Sham AK wk 3 = 1.45 (0.74)/ FU wk</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other *Bech-Rafaelsen Melancholia scales (MES) reported NOT BDI MES Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.73 (0.12 - 1.33), P = 0.03; Awk 3 Effect size (95% CI) and Mann- Whitney P: 0.84 (0.24 -1.46), P = 0.00; FU wk 5 Effect size (95% CI) and Mann- Whitney P: 0.64(0.02 -1.22), P = 0.03; FU wk 8 Effect size (95% CI) and Mann- Whitney P: 0.65 (0.04 - 1.24), P = 0.03; FU wk 12 Effect size (95% CI) and Mann- Whitney P: 0.46 (- 0.12 - 1.06), P = 0.12;</p>	<p>12 =0.94 (0.73); rTMS A wk = 1.27 (0.94), FU wk 12 0.71(0.56); Dry Mouth: Sham AK wk 3 = 0.43 (0.56)/ FU wk 12 = 0.11 (0.32); rTMS A wk 3 = 0.27 (0.46), FU wk 12 0.14(0.36); Micturia: Sham AK wk 3 = 0.09 (0.29)/ FU wk 12 = 0.00 (0.00); rTMS A wk 3 = 0.05 (0.22), FU wk 12 0.00 (0.00);</p> <p>Adequate information Yes</p> <p>Attrition Overall, % 3 RTMS patients did not complete protocol, and 1 sham patient did not complete (analysis used last observation carried forward). At 3 week outcome, all 45 patients in m-ITT were present. By end of study at 12 weeks, 6/49 (12%) had dropped out.</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p><i>MADRS</i> NR</p> <p><i>IDS</i> NR</p> <p><i>CGI-S</i> NR</p> <p><i>CGI-I</i> NR</p> <p>Instrument</p> <p>Major Depression Inventory (MDI)</p> <p>Baseline n G1: n @ baseline = 25; M-ITT = 23 G2: n@ baseline = 24; M-ITT = 22</p> <p>Baseline score, mean (SD) G1: 33.5 (5.1) G2: 34.0 (5.6)</p> <p>Endpoint score, mean (SD) G1: A wk 2 = 23.8 (9.0), A wk 3 = 21.5 (9.8), FU wk 5 = 20.1 (9.0), FU wk 8 = 18.4 (10.0), FU wk 12 = 16.1 (10.7)</p>	<p>At end of treatment, % G1: At end of rTMS (3 wks) = 0 G2: At end of Sham (3 wks) = 0</p> <p>At end of follow-up, % G1: 21% G2: 4%</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Adherence/ compliance NR</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>G2: A wk 2 = 27.9 (10.6), A wk 3 = 26.6 (9.9), FU wk 5 = 23.7 (9.5), FU wk 8 = 21.5 (11.0), FU wk 12 = 19.6 (12.8)</p> <p>Change, mean (SD) G1: 17.4 G2: 14.4</p> <p>MDI Awk 2 Effect size (95% CI) and Mann-Whitney P = 0.36 (-0.23 - 0.94), P = 0.18; Awk 3 Effect size (95% CI) and Mann-Whitney P:0.43 (-0.16 - 1.03), P = 0.29; FU wk 5 Effect size (95% CI) and Mann-Whitney P: 0.29 (-0.29 - 0.88), P =0.20; FU wk 8 Effect size (95% CI) and Mann-Whitney P: 0.22 (-0.36 - 0.81), P = 0.72; FU wk 12 Effect size (95% CI) and Mann-Whitney P: 0.23 (-0.36 -0.81), P = 0.43;</p>	

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Holtzheimer et al., 2004¹⁹</p> <p><i>Country, setting</i> USA, single center, outpatient/inpatient status not clearly stated</p> <p><i>Funding</i> University of Washington</p> <p><i>Research Objective</i> Initial hypotheses that rTMS would have greater antidepressant effects than sham stimulation and that rTMS would be safe and tolerable</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 15</p> <p><i>Duration</i> Primary endpoint following 2 weeks of treatment and follow-up 1 week after txt completed</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> All pts discontinued (failed) AD medication</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains:32 • Length of train (seconds): 5 • Inter-train interval: 30-60</p>	<p><i>TRD definition</i> • Subjects must have failed at least two previous antidepressant trials due to lack of response to an adequate trial (defined by ATHF) or medication intolerance • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • 21 to 65 years of age • Right-handed • Meet DSM-IV criteria for a major depressive episode due to MDD • HAM-D17 ≥ 18</p> <p><i>Exclusion criteria</i> • No other major psychiatric or medical comorbidity • History of Bipolar Disorder • Previous failure of ECT • History of substance abuse or dependence • Current symptoms of psychosis • Pregnancy</p>	<p><i>Treatment Failure</i> Failed 7 or more, % G1: 85.7 G2: 37.5</p> <p><i>Polarity, %</i> Unipolar 100% MDD</p> <p><i>Age, mean yrs</i> G1: 40.4 G2: 45.4</p> <p><i>Sex, % females</i> G1: 57.1 G2: 42.9</p> <p><i>Right handed, %</i> G1: 100 G2: 100</p> <p><i>HAM-D 17</i> Baseline n G1: 7 G2: 8</p> <p>Baseline score, mean (SD) G1: 22.7 (5.3) G2: 20.8 (6.3)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 29.6 (10.0) G2: 28.5 (10.6)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) At week 1 G1: 18.0 (1.2) G2:18.0 (2.7)</p> <p>At week 2 G1: 14.6 (3.2) G2: 15.3 (3.0)</p> <p>1 week follow-up G1: 18.8 (2.5) G2: 17.6 (2.1)</p> <p>Change, mean (SD) At week 1 G1: 4.7 G2: 2.8</p> <p>At week 2 G1: 8.1 G2: 5.5</p> <p>1 week follow-up G1: 3.9 G2: 3.2 All endpoints, <i>P</i> = NS</p> <p>Responders, n (%) At week 1 G1: 0 G2: 0</p> <p>At week 2 G1: 2 (28.6) G2: 1 (12.5)</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p> <p><i>Neuropsychological or executive functioning</i> Both groups performed equally well with exception of one measure of verbal memory, Trial 7 of Rey Auditory Verbal Learning Test, in which subjects that received rTMS performed slightly better (rTMS: mean score = 12.7 (2.1) vs.: sham mean score = 12.0 (2.3); <i>P</i> < 0.05). No acute changes in level of consciousness, orientation, or short-term memory associated with any rTMS or sham treatments sessions.</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Pulses per session: 1600 • Total number of sessions: 10 over 2 wks <p>Sham rTMS</p> <ul style="list-style-type: none"> • Delivered in same anatomical location with identical stimulation parameters, but with lateral edge of coil rotated 45 degrees away from scalp 			<p>1 week follow-up G1: 0 G2: 0</p> <p><i>BDI</i> Endpoint score, mean (SD) At week 1 G1: 27.5 (3.2) G2: 24.9 (2.7)</p> <p>At week 2 G1: 23.9 (2.6) G2: 22.4 (2.4)</p> <p>1 week follow-up G1: 23.9 (1.6) G2: 26.4 (1.9)</p> <p>Change, mean (SD) At 2 weeks G1: 5.7 G2: 6.1</p> <p>Change, mean (SD) 1 week follow-up G1: -5.7 G2: -2.1 Group x time (all points), <i>P</i> = NS</p>	<p><i>MMSE</i> NR There were no major adverse events at any point in study. Some subjects experienced mild pain with active rTMS, but treatments were generally well tolerated.</p> <p><i>Attrition</i> Overall, % 0 during treatment. 3 (20%) before final assessment at week 3</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % G1: 28.6 G2: 12.5</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p>Other NR</p>

Evidence Table 31. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<i>Adherence/ compliance</i> Compliance All 15 subjects completed all 10 txt sessions

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Boutros et al., 2002¹³</p> <p><i>Country, setting</i> US, Yale School of Medicine and VA-Connecticut, outpatient</p> <p><i>Funding</i> VA Merit Award & K24 DA00520-01A1/DA/NIDA NIH HHS; 1 author employee of Pfizer</p> <p><i>Research Objective</i> To provide additional data on efficacy and safety for rTMS as an augment strategy in TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 21</p> <p><i>Duration</i> 2 weeks txt; follow-up with responders for up to 20 weeks post txt</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> Pts allowed to continue all current psychotropic meds</p> <p><i>Strategy</i> Augmentation, 3 pts in active and 1 in sham txt were not on any meds</p> <p><i>Parameters</i> rTMS: • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • 2+ failed trials of adequate dose and durations • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major Depression • HAM-D25 >= 20</p> <p><i>Exclusion criteria</i> • Suicidality • "Prominent" psychotic symptoms • History of neurological disorders • current drug abuse</p>	<p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100%</p> <p><i>Age, mean yrs</i> G1: 49.5 G2: 52.0</p> <p><i>Sex, % females</i> G1: 25 G2: 10</p> <p><i>Right handed, %</i> G1: 90.9 G2: 88.9</p> <p><i>HAM-D Baseline n</i> G1: 12 G2: 9</p> <p><i>Baseline score, mean (SD)</i> G1: 34.4 (10.1) G2: 31.7 (4.9)</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) At 2 weeks G1: 29.0 G2: 28.11</p> <p><i>Change, mean (SD)</i> G1: -11.75 G2: -6.22 P = NS</p> <p><i>Responders, n</i> Defined as 30% improvement on HAM-D G1: 7 G2: 2</p> <p><i>Responders, n (%)</i> Defined as 50% improvement on HAM-D G1: 3 G2: 2</p> <p><i>Relapse</i> Of 6 active treatment responders included in 20-week follow-up (no continuing intervention), 4 relapsed. Of 1 sham responder included in thh 20-week follow-up, 1 relapsed.</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: (% of pts reporting AEs) 66.7 G2: 55.6</p> <p><i>Cognitive impairment, %</i> Difficulty concentrating (phase 1 only) G1: 25 G2: NR</p> <p><i>Headache, %</i> "most frequent complaint" % NR Other: • scalp tenderness at site of stimulation: 25%, 11.1% • hearing problem: 8.3%, NR; • diarrhea: 8.3%, NR</p> <p><i>Attrition</i> Overall, % 18.2% (4/22)</p> <p><i>At end of treatment, %</i> G1: 8.3 (1/12) G2: 30.0 (3/10)</p> <p><i>At end of follow-up, %</i> NR</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Inter-train interval: 58 Pulses per session: 800 Total number of sessions: 10 over 10 weekdays Sham: <ul style="list-style-type: none"> Coil angled 90 degrees to scalp 1 wing of figure 8 touching scalp 				Withdrawals due to efficacy, %: NR Withdrawals due to adverse events, %: NR <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Fitzgerald et al., 2006¹⁴</p> <p><i>Country, setting</i> Australia, single center</p> <p><i>Funding</i> Australian National Health and Medical Research Council and by Constance and Stephen Lieber through a National Alliance for Research on Schizophrenia and Depression Lieber Young Investigator award (to Dr. Fitzgerald)</p> <p><i>Research Objective</i> rTMS versus placebo for depression</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT (LOCF)</p> <p><i>N</i> 50</p> <p><i>Duration</i> 2 wks double blind with those with >20% decrease in MADRS to continue treatment for up to 6 wks with active or sham txt (LOCF for all pts); sham pts with inadequate response were allowed to enter open label txt. Primary outcome after 2 and 6 weeks of txt</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> 2+ failed medications with txt duration ≥6 wks Not required or not specified to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> DSM-IV diagnosis of Major Depressive Episode MADRS ≥ 20 <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> Significant medical illness Neurological disorders Other axis I psychiatric disorders 	<p><i>Treatment Failure</i></p> <p>Mean failed AD trials (lifetime)</p> <p>G1: 5.6 (3.1) G2: 6.2 (3.0)</p> <p><i>Polarity, %</i></p> <p>Unipolar G1: 84% G2: 84%</p> <p>Bipolar G1: 16% G2: 16%</p> <p><i>Age, mean yrs</i></p> <p>G1: 46.8 G2: 43.7</p> <p><i>Sex, % females</i></p> <p>G1: 60 G2: 64</p>	<p>HAM-D 17 Endpoint score, mean (SD) NR</p> <p>Change, % decrease (SD) G1: 45.2% (40.1) G2: 5.4% (23.1) <i>P</i> < 0.001</p> <p>Change, mean G1: -10.17 G2: -1.07</p> <p>Responders, n (%) At 6wks G1: 13 (52.0) G2: 2 (8.0) <i>P</i> = 0.001</p>	<p><i>Quality of Life</i></p> <p>GAF Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 48.8 (8.2) G2: 49.0 (4.9)</p> <p>Endpoint score, mean (SD) G1: 59.0 (16.5) G2: 50.1 (10.3) [<i>P</i> <0.05]</p> <p>Change, mean (SD) G1: 10.2 G2: 1.1 GAF Scale (t=2.0, df=40.2, <i>P</i> < 0.05)</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Quality Rating</i> Good</p>	<p><i>Interventions</i> G1: rTMS G2: Sham <i>Medications allowed</i> • Stable medications allowed • SSRIs, SNRIs, Tricyclics ADs • Mood stabilizers, • Lithium, • Anticonvulsants, • Antipsychotic medication, • Benzodiazepines</p> <p><i>Strategy</i> Augmentation, 23% not taking medication at study entry</p> <p><i>Parameters</i> rTMS Low Right: Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 3 • Length of train (seconds): 140 • Inter-train interval: 180 • Pulses per session: 420 Sequential High Left: • Frequency (Hz): 10 • Motor threshold (%): 100 • Number of trains: 15</p>		<p>HAM-D 17 Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 22.5 (7.4) G2: 19.8 (4.4)</p> <p>BDI Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 29.2 (18.3) G2: 29.3 (9.9)</p> <p>MADRS Baseline n G1: 25 G2: 25</p> <p>Baseline score, mean (SD) G1: 34.0 (5.9) G2: 34.1 (5.2)</p>	<p>Remitters, n At 6wks G1: 10 (40.0) G2: 0 (0) <i>P</i> = NR BDI</p> <p>Endpoint score, mean (SD) At week 2 G1: 18.3 (10.3) G2: 221.6 (13.7)</p> <p>At 4 weeks G1: 10.5 (8.3) G2: 21.0 (19.8)</p> <p>At 6 weeks G1: 9.2 (6.7) G2: NR</p> <p>Change, mean (SD) At week 2 G1: 10.9 G2: 7.7</p> <p>At 4 weeks G1: 18.7 G2: 8.3</p> <p>At 6 weeks G1: 20.0 G2: NR, <i>P</i> = 0.01</p> <p>Responders, n NR</p>	<p><i>Adverse Events</i> Headache, % G1: 20 G2: 8 Nausea 12% vs. 0, No seizures or manic episodes; Hopkins Verbal Learning Test performance decreased for both groups with no group by time interaction. Performance improved on digit span backward test improved in rTMS only (group by time: <i>P</i> = 0.07). Controlled Oral Word Association test improved for both groups (time: <i>P</i> = 0.001). Nausea 12% vs. 0, No seizures or manic episodes;</p> <p><i>Neuropsychological or executive functioning</i> Hopkins Verbal Learning Test Performance decreased for both groups with no group by time interaction Digit span backward Test Performance improved in rTMS only (group by time: <i>P</i> = 0.07).</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 750 • Total number of sessions: 10 sessions/day, 5 days/wk <p>Sham:</p> <ul style="list-style-type: none"> • Coil angled at 45 degrees off head. Medial wing of coil was resting on scalp • Stimulation parameters identical to those for active treatment (both sides) 			<p>Remitters, n NR</p> <p>MADRS Endpoint score, mean (SD) At week 2 G1: 26.2 (10.2) G2: 30.9 (8.2)</p> <p>At week 4 G1: 11.7 (7.1) G2: 34.5 (12.0)</p> <p>At week 6 G1: 8.9 (7.9) G2: NA</p> <p>Change, mean (SD) At week 2 G1: 7.8 G2: 3.2</p> <p>At week 4 G1: 22.3 G2: 0.4 (increased)</p> <p>At week 6 G1: 25.1 G2: NA</p> <p>Group by time, $P = 0.001$ at all time points</p> <p>Responders, n At 6 weeks G1: 11</p>	<p>Controlled Oral Word Association Test Improved for both groups $P = 0.001$</p> <p>MMSE NR</p> <p><i>Other</i> Nausea 12% vs. 0 No seizures or manic episodes;</p> <p><i>Attrition</i> Overall, % At 2 weeks: 6 At 3 weeks: 56 At 4 weeks: 70 At 5 weeks: 78 At 6 weeks: 78 After initial 2 weeks, patients that did not have a 10% reduction on a weekly assessment were withdrawn</p> <p>At end of treatment, % G1: 0 G2: 12</p> <p>At end of follow-up, % G1: 56 G2: 100</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				G2: 2 $P < 0.05$ Remitters, n MADRS < 10 At 6 weeks G1: 9 G2: 0 $P = 0.005$ At week 2 G1: 2 G2: 0 Follow-up at week 3 G1: 3 G2: 0 Follow-up at week 4	Withdrawals due to efficacy, % NR Withdrawals due to adverse events, % NR <i>Adherence/ compliance</i> NR
<p><i>Author, Year</i> Fitzgerald et al., 2003¹⁵</p> <p><i>Country, setting</i> Australia 2 general psychiatric services, outpatients</p> <p><i>Funding</i> National Health and Medical Research Council and a grant from Stanley Medical Research Institute</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 60 Tier 1</p> <p><i>Duration</i> Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow-up</p>	<p><i>TRD definition</i> • Failed a minimum of 2 courses of antidepressant medications (6+ weeks)</p> <p>Not required or not specified to be in current episode</p> <p><i>Inclusion criteria</i> • DSM-IV diagnosis of Major Depression (included bipolar depression)</p>	<p><i>Treatment Failure</i> Mean failed trials Overall (SD) 5.68 (3.40) Polarity, %</p> <p>Bipolar I G1: 5 G2: 5 G3: 20</p> <p><i>Age, mean yrs</i> G1: 42.2 G2: 45.55 G3: 49.15</p>	<p>BDI Endpoint score, mean (SD)</p> <p>At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7)</p> <p>Change, mean (SD) At 2 weeks G1: -6.4 G2: -7.8 G3: -2.3 $P = 0.03$</p>	<p><i>Quality of Life</i> GAF Global Assessment of Functioning</p> <p>Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Research Objective</i> To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group</p> <p><i>Quality Rating</i> Good</p>	<p>assessment conducted at 2 weeks post txt.</p> <p><i>Interventions</i> G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham</p> <p><i>Medications Allowed</i> 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood stabilizers and antipsychotics</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week</p>	<p><i>Exclusion criteria</i> • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders</p>	<p><i>Sex, % females</i> G1: 40 G2: 35 G3: 55</p> <p><i>Right handed, %</i> G1: 90 G2: 100 G3: 85</p> <p>BDI Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)</p> <p>MADRS Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)</p>	<p>MADRS Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5)</p> <p>Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5 % (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) P = 0.004 G1: vs. G3, G2 vs. G3, P < 0.005</p> <p>Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) P = 0.07</p> <p>Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 P = NR</p>	<p>Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8)</p> <p>Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5</p> <p>Overall group F56,2=2.6; P =.08; LFR-TMS vs sham: P = 0.03; and HFLTMS vs sham: P = 0.09</p> <p><i>Quality of Life</i> Overall group F56,2=2.6; P =.08; LFR-TMS vs sham: P = 0.03; and HFLTMS vs sham: P = 0.09</p> <p><i>Adverse Events</i> Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3% Other: 0- 2wks: 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>rTMS High</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week <p>Sham rTMS</p> <ul style="list-style-type: none"> • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week 			<p>CGI Endpoint score, mean (SD) NR <i>P</i> =.01</p>	<p>(10%) reported a headache after rTMS. Although there was no difference in incidence of these adverse effects (<i>P</i> =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour. Two patients (1 in each group) reported transient dizziness for a short time after treatment. 2wks - 4 wks: One patient withdrew after 1 session of HFL-TMS treatment insingle-blind phase ofstudy owing to site pain. One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Neuropsychological or executive functioning</i></p> <ul style="list-style-type: none"> • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions • Including all patients who underwent at least 1 type of active treatment, there was a significant improvement in performance on verbal paired associates ($t_{50}=-7.3$; $P < 0.001$), verbal fluency ($t_{48}=-3.8$; $P < 0.001$), and digit span forwards ($t_{48}=-1.8$; $P = 0.003$) subscales; Personal Semantic Memory Schedule ($t_{50}=-2.4$; $P = 0.02$); and Autobiographical Memory Schedule ($t_{50}=-1.9$; $P = 0.05$). • A similar pattern of improvements was seen for each of treatment subgroups (HFL-TMS

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>only, LFR-TMS only, or both active treatments).</p> <ul style="list-style-type: none"> Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across same times. <p>MMSE NR</p> <p><i>Other</i></p> <p><i>Attrition</i> Overall, % None in initial 2 week treatment phase</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % NR But at least 28.3% did not continue on thru 2nd 2 weeks</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, %</p>

Evidence Table 32. KQ 4. Adherence: Tier 1 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					G1: 0 (1 during follow-up) G2: 0 (0 during follow-up) G3: 0 (0 during follow-up) Progression of patients through 2nd phase is very unclear <i>Adherence/ compliance</i> NR

Evidence Table 33. KQ 4. Adherence: Tier 1 (ECT vs. pharma—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Folkerts et al., 1997⁴²</p> <p><i>Country, setting</i> Germany, single center, inpatients</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To compare ECT in a controlled, randomized study with serotonin reuptake inhibitor paroxetine in treatment-resistant depression.</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> per protocol</p> <p><i>N</i> 39</p> <p><i>Duration</i> Total 6 weeks; Wash-out >= 3days; Phase I ECT - 2wks, Paroxetine - 4 wks; Phase II Paroxetine group - if clinical improvement reduction < 50% treatment switched to ECT, ECT group crossed over to Paroxetine or other antidepressants.</p> <p><i>Interventions</i> G1: ECT G2: Paroxetine</p> <p><i>Medications Allowed</i> After med wash -out patients were allowed a tranquillizer (diazepam up to 5 mg daily), a sedative (lormetazepam 0.5- 1.0 mg or triazolam 0.25 mg) or a sedative neuroleptic</p>	<p><i>TRD definition</i> • 2+ failed treatmentd (8+ weeks) including at least 1 tricyclic, at a dosage of at least 100 imiprimine equivalents • Not required or not specified to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Major depressive episode single and recurrent • Bipolar disorders • HAM-D21 >=22</p> <p><i>Exclusion criteria</i> • Psychosis • Pronounced suicidal tendency • Severe physical illness • History of substance abuse • previous paroxetine or ECT treatment</p>	<p><i>Treatment Failure</i> Level of tx resistance (Kuhs, 1995) G1: 1.9 (0.7 SD) G2: 2.0 (0.8 SD)</p> <p>Mean failed trials G1: 4.9 G2: 4.3</p> <p><i>Polarity, %</i> Unipolar G1: 90.5 G2: 83.3</p> <p>Bipolar G1: 9.5 G2: 16.7</p> <p><i>Age, mean yrs</i> G1: 47.6 G2: 52.3</p> <p><i>Sex, % females</i> G1: 62 G2: 44</p> <p>HAM-D 21 Baseline n G1: 21 G2: 18</p> <p>Baseline score, mean (SD) G1: 31.1 (4.9) G2: 32.6 (5.4)</p>	<p>HAM-D 21 Endpoint score, mean (SD) Endof Phase I (ECT: 2-3 wks, Paroxetine: 4 wks) G1: 12.5 (3.9) G2: 23.0 (10.4) Endof Phase II (open trial, 6 weeks) G1: 12.8 (5.1) G2: 15.2 (7.9)</p> <p>Change, mean (SD) End of Phase I G1: -18.6 G2: -9.6 % Reduction in HAM-D, <i>P</i> = 0.001 End of Phase II G1: 18.3 G2: 17.4</p> <p>Responders, n End of Phase I G1: 15 (71.4%) G2: 5 (27.8%) <i>P</i>= 0.006</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 0 - all patients continued to scheduled end of treatment</p> <p>At end of treatment, % 0</p> <p>At end of follow-up, % 0</p> <p>Withdrawals due to efficacy, % 0</p> <p>Withdrawals due to adverse events, % 0</p> <p><i>Adherence/ compliance</i> • All pts continued their respective therapies through scheduled end of treatment Phase I • 11 of 21 ECT were able to discontinue after 6th ECT session and 10 pts. had 3</p>

Evidence Table 33. KQ 4. Adherence: Tier 1 (ECT vs. pharma—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>(pipamperon, up to 40 mg daily).</p> <p><i>Parameters</i> ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 0 • Intensity: 2.5-fold seizure threshold • Number of sessions (range, mean, SD): 3/wk, range 6 to 9, mean 7.2 session <p>Paroxetine</p> <ul style="list-style-type: none"> • Started at 20 mg/day, within 7 days increased to 40 mg, allowed up to 50 mg, mean dose 44 mg/day for at least 4 weeks <p><i>Strategy</i> Switch</p>				<p>additional ECT treatments.</p> <ul style="list-style-type: none"> • Phase II - of ECT group, 9 received paroxetine and 12 received other antidepressants • Of paroxetine groups, 7 crossed over to ECT • 11 received antidepressants - 7 paroxetine and 4 received other antidepressants <p>1 person was excluded from analysis due to failure to increase treatment dosage</p>

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Stern et al., 2007³²</p> <p><i>Country, setting</i> NR, outpatient setting</p> <p><i>Funding</i> The Milton Fund, NARSAD, Stanley Vada NAMI Foundation, NIMH, Spanish Ministerio de Educacion y Ciencia</p> <p><i>Research Objective</i> To test hypothesis that rTMS exerts antidepressant effects either by enhancing left dorsolateral prefrontal cortex (DLPFC) excitability (using high-frequency rTMS) or by decreasing right DLPFC excitability (using low-frequency rTMS) have equivalent an</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in the analysis</p> <p><i>N</i> 45</p> <p><i>Duration</i> • 10 days (2 wk) stimulation and 2 wk f/u for all 4 gps • An additional 2 wk of unblinded f/u with gp 1 & 3 to assess for relapse.</p> <p>Primary Outcome: HAM-D at 2 weeks and 2 weeks after treatment</p> <p><i>Interventions</i> G1: 10 Hz rTMS to left DLPFC G2: 1 Hz rTMS to left DLPFC G3: 1 Hz to right DLPFC G4: Sham rTMS</p> <p><i>Medications allowed</i> No psychotropic medications were allowed</p>	<p><i>TRD definition</i> • All referred for ECT having failed an adequate course of antidepressant med • Required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Patients w unipolar recurrent major depressive disorder (SCID & DSM-IV) HAM-D21 score ≥ 20</p> <p><i>Exclusion criteria</i> • H/O any psychotic disorder (incl. schizophrenia or schizoaffective disorder) • Bipolar disorder • Obsessive compulsive disorder • Personality disorder • SA(except nicotine) within past yr • Current acute/chronic medical condition requiring txt with psychoactive medication • H/O epilepsy or unprovoked seizures or other neurological disorder</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar 100 % MDD</p> <p><i>Age, mean yrs</i> G1: 53.2 G2: 52.3 G3: 52.8 G4: 53.3</p> <p><i>Sex, % females</i> G1: 60 G2: 60 G3: 70 G4: 60</p> <p><i>Right handed, %</i> 100</p> <p><i>HAM-D 21</i></p> <p>Baseline n G1: 10 G2: 10 G3: 10 G4: 15</p> <p>Baseline score, mean (SD) G1: 27.8 (3.2) G2: 27.6 (3.9) G3: 27.9 (3.8) G4: 27.4 (2.9)</p>	<p><i>HAM-D 21</i> Endpoint score, mean (SD) At week 1 G1: 22.2 (5.6) G2: 27.6 (5.9) G3: 20.9 (4.1) G4: 25.6 (4.5)</p> <p>At week 2 G1: 15.1 (6) G2: 27.6 (5.9) G3: 15.8 (4.8) G4: 26.7 (3.6)</p> <p>Week 1 Follow-up G1: 12.8 (5.7) G2: 26.4 (2.3) G3: 15.3 (6.4) G4: 26.5 (2.3)</p> <p>Week 2 Follow-up G1: 13.4 (5.6) G2: 26.6 (3.0) G3: 14.9 (5.9) G4: 26.8 (2.3)</p> <p>Change, mean (SD) At week 2 G1: -12.7 G2: 0.0 G3: -12.1 G4: -0.7 % change, <i>P</i> = 0.001</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> 9/45 pts reported severe headaches (pts by group NR); no seizures</p> <p><i>Attrition</i> Overall, %: 17.8</p> <p>At end of treatment, % G1: 0 G2: 20 G3: 0 G4: 10</p> <p>At end of follow-up, % G1: 0 G2: 50 G3: 0 G4: 20</p> <p>Withdrawals due to efficacy: NR</p> <p>Withdrawals due to adverse events, % G1: 0 G2: 50 G3: 0 G4: 20 Though 8 pts withdrew due to AE, only 3 of those were listed as w/d during active period.</p>

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> rTMS High Frequency: • Frequency (Hz):10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 52 • Pulses per session: 1600 • Total number of sessions: 10 days</p> <p>Low Frequency LDLPFC: • Frequency (Hz):1 • Motor threshold (%): 110 • Number of trains: 1 • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days</p> <p>Low Frequency RDLPFC: • Frequency (Hz): 1 • Motor threshold (%): 110 • Number of trains: 1</p>	<ul style="list-style-type: none"> • Abnormal neurological examination • Family H/O medication-resistant epilepsy • Prior brain surgery • Metal in head • Implanted medical device • Pregnancy 		<p>2 week follow-up G1: 0 G2: 1.0 G3: 13.0 G4: 0.6 % change, $P = 0.00001$</p> <p>Responders, n At week 1 G1: 0 G2: 0 G3: 0 G4: 0</p> <p>At week 2 G1: 2 (50%) G2: 0 (0%) G3: 5 (50%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>1 week follow-up G1: 6 (60%) G2: 0 (0%) G3: 6 (60%) G4: 0 (0%) G1/G3 vs. G2/G4 ($P < 0.0005$)</p> <p>2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 6 (6%) G4: 0</p>	<p>Reported in text as dropped out following week 2.</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Length of train (seconds): 1600 • Inter-train interval: 1 • Pulses per session: 1600 • Total number of sessions: 10 days Sham rTMS: <ul style="list-style-type: none"> • Orientation of coil perpendicular to scalp subdivided into 3 groups, replicating parameters for each group above Strategy Switch			G1/G3 vs. G2/G4 ($P < 0.0005$) Remitters, n HAM-D \leq 10 At week 1 G1: 0 (0%) G2: 0 (0%) G3: 0 (0%) G4: 0 (0%) At week 2 G1: 3 (30%) G2: 0 (0%) G3: 1 (10%) G4: 0 (0%) 1 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) 2 week follow-up G1: 4 (40%) G2: 0 (0%) G3: 3 (30%) G4: 0 (0%) Responders followed for additional two weeks (endpoint 2wk follow-up) G1: vs. G3 $P = NS$ (all times); G2 vs. G4 and G1: vs. G3 $P = NS$ (all times)	

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> O'Reardon, 2007³¹</p> <p><i>Country, setting</i> US, Canada, Australia; multicenter, outpatient/inpatient status not clearly reported</p> <p><i>Funding</i> Neuronetics</p> <p><i>Research Objective</i> To test whether transcranial magnetic stimulation (TMS) overleft dorsolateral perfrontal cortex is effective and safe in acute treatment of major depression</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Modified ITT (m-itt)</p> <p><i>N</i> 325 randomized</p> <p><i>Duration</i> 6 weeks; Primary efficacy outcome (MADRS) collected at wk4. Sham patients could cross over after 4 weeks if not responding.</p> <p><i>Interventions</i> G1: Active TMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients were free of ADs and other psychotropic medications directed at treating depression. Pts allowed only limited use of hypnotics, anxiolytics for treatment emergent insomnia or anxiety</p> <p><i>Strategy</i> Switch</p>	<p><i>TRD definition</i> • Specifically required to have failed at least one in this or most recent episode OR four failed attempts in a lifetime</p> <p><i>Tier 2 Setting(s)</i> Not clearly reported</p> <p><i>Inclusion criteria</i> • Aged 18–70 • DSM-IV diagnosis of MDD • Single episode or recurrent, with a current episode duration ≤3 • CGI-S score ≥ 4 • HAM-D17 ≥ 20 Symptom stability during a 1-week no-treatment lead-in period, with a HAM-D17 total score of at least 18 and a decrease in score of 25% or less from that observed at screening assessment</p> <p><i>Exclusion criteria</i> • A lifetime history of psychosis, bipolar disorder, or obsessive–compulsive disorder</p>	<p><i>Baseline N</i> G1: 165 G2: 160 Current episode failures, mean G1: 1.6 G2: 1.6</p> <p>Mean failed trials NR</p> <p>Previous treatment, not specified, % NR</p> <p><i>Polarity, %</i> Unipolar 100</p> <p><i>Age, mean yrs</i> G1: 47.9 G2: 48.7</p> <p><i>Sex, % females</i> G1: 55.5% G2: 50.7%</p> <p><i>Race, % white</i> G1: 94.2% G2: 89.7%</p> <p>HAM-D 17 Baseline score, mean (SD) G1: 22.6 (3.3) G2: 22.9 (3.5)</p>	<p>HAM-D 17 Analyzed n G1: 155 G2: 146</p> <p>Endpoint score, mean (SD) At week 4 G1: 17.4 (6.5) G2: 19.4 (6.5) At week 6 G1: 17.1 (7.7) G2: 19.6 (7.0)</p> <p>Change, mean (SD) At week 2 G1: -5.2 G2: -3.5</p> <p>At week 6 G1: -5.5 G2: -3.3 P = 0.005</p> <p>Responders, n (%) At week 2 G1: 18 (11.6) G2: 13 (8.9) P > 0.10</p> <p>At week 4 G1: 32 (20.6) G2: 17 (11.5) P < 0.05</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Serious adverse events G1: 6 G2: 5</p> <p>Suicidality, % G1: 0.6 G2: 1.9</p> <ul style="list-style-type: none"> • Exacerbation of depression: active TMS = 0.6%, sham TMS = 1.9% • Eye pain: active TMS = 6.1% sham TMS = 1.9%; • GI disorders toothache: active TMS = 7.3%, sham TMS = 0.6%; • Application site discomfort: TMS = 10.9%, sham = 1.3% • Application site pain, %: TMS = 35.8, sham = 3.8 • Facial pain: active TMS = 6.7%, sham TMS = 3.2 • Muscle twitching: TMS = 20.6%, sham = 3.2% • Pain of skin: TMS = 8.5%, TMS = 0.6%

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 120 • Number of trains: 75 • Length of train (seconds): 4 • Inter-train interval: 26 • Pulses per session: 3000 • Total number of sessions: 5/week for 4-6 wks <p>rTMS Sham:</p> <ul style="list-style-type: none"> • Coil has embedded magnetic shield, limiting magnetic energy reaching cortex to 10% or less than active coil 	<ul style="list-style-type: none"> • Posttraumatic stress disorder and eating disorders (if present in past year) • Lack of response to an adequate trial of electroconvulsive therapy (ECT) • Prior treatment with TMS or a vagus nerve stimulator implant • Pregnancy • Personal or close family history of seizure disorder • Presence of neurologic disorder or medication therapy known to alter seizure threshold • Presence of ferromagnetic material in or in close proximity to head 	<p>MADRS Baseline n G1: 155 G2: 146</p> <p>Baseline score, mean (SD) G1: 32.8 (6.0) G2: 33.9 (5.7)</p> <p>IDS Baseline n G1: 155 G2: 146</p> <p>Baseline score, mean (SD) G1: 42.0 (9.4) G2: 43.4 (9.9)</p> <p>CGI-S Baseline n G1: 155 G2: 146</p> <p>Baseline score, mean (SD) G1: 4.7 (.6) G2: 4.7 (.7)</p>	<p>At week 6 G1: 38 (24.5) G2: 20 (13.7) <i>P</i> < 0.05</p> <p>Remission rate n (%) HAM-D17 < 8 At week 2 G1: 5 (3.2) G2: 3 (2.1) <i>P</i> > 0.10</p> <p>At week 4 G1: 110 (7.1) G2: 9 (6.2) <i>P</i> > 0.10</p> <p>At week 6 G1: 24 (15.5) G2: 13 (8.9) <i>P</i> = 0.065</p> <p>MADRS Endpoint score, mean (SD) At 4 weeks G1: 27 (11.1) G2: 29.8 (10.1) At 6 weeks G1: 26.8 (12.8) G2: 30 (10.8)</p> <p>Change, mean (SD) At 4 weeks G1: 5.8 G2: 4.1</p>	<p>MMSE NR</p> <p><i>Attrition</i> Overall, % 15</p> <p>At end of treatment, % G1: wk2 6%/ wk 4 5% G2: wk 2 9%/ wk 4 6%</p> <p>At end of follow-up, % G1: NR G2: NR</p> <p>Withdrawals due to efficacy, % G1: 0.6% G2: 1%</p> <p>Withdrawals due to adverse events, % G1: 5% G2: 4%</p> <p>Other</p> <ul style="list-style-type: none"> • 325 subjects were randomized • 24 were "nonevaluable" • 301 continued to receive at least 1 treatment, these 301 were included in final analysis • 277 completed study through week 4.

Evidence Table 34. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD only) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>At 6 weeks G1: 6 G2: 3.9</p> <p><i>Response rate, %</i> At week 2 G1: 8.4 G2: 6.2 <i>P</i> > 0.10 At week 4 G1: 18.1 G2: 11.0 <i>P</i> <0.05 At week 6 G1: 23.9 G2: 12.3 <i>P</i> <0.01</p> <p>Remission rate, % Remission defined as total score <10 At week 2 G1: 3.9 G2: 2.1 <i>P</i> > 0.10</p> <p>At week 4 G1: 7.1 G2: 6.2 <i>P</i> > 0.10</p> <p>At week 6 G1: 14.2 G2: 5.5 <i>P</i> < 0.05</p>	<p><i>Adherence/ compliance</i> NR</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Berman et al., 2000²⁸</p> <p><i>Country, setting</i> US, urban community health center, inpatient and outpatients</p> <p><i>Funding</i> Veterans Administration, NIMH, State of CT Research Objective To assess efficacy of rTMS in unmedicated TRD patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> 2 weeks (10 weekdays of txt) Primary outcome = HAM-D at 2wks</p> <p><i>Interventions</i> G1: rTMS G2: Sham TMS</p> <p><i>Medications Allowed</i> All patients free of antidepressants, neuroleptics, and benzodiazepines Inpatients pts allowed chloral hydrate for sleep</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS – • Frequency (Hz): 20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • 1+ failed trials (4+ weeks duration with at least 200 mg mg/d of imipramine, 20mg/day fluoxetine, 60mg/d phenelzine, 225mg/d venlafaxine, 30mg/d mirtazapine) • Not required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • Current Major depressive episode (via Ham-D)</p> <p><i>Exclusion criteria</i> • Hx of sig. neurological illness • EEG abnormalities suggestive of an epileptic predisposition • Substance or alcohol use abuse diagnosis, • Sig. unstable medical illness, • Females - pregnancy or inadequate birth control</p>	<p><i>Treatment Failure</i> Current episode failures, mean G1: 5 G2: 3.5 (+ a median of 1 aumgmentation in eachgroup)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 90</p> <p>Bipolar II G1: 0 G2: 10</p> <p><i>Age, mean yrs</i> G1: 45.2 G2: 39.4</p> <p><i>Sex, % females</i> G1: 20 G2: 40</p> <p><i>Race, % white</i> G1: 100 (n=1 hispanic) G2: 100 (n=1 hispanic)</p> <p><i>HAM-D 25</i> Baseline n G1: 10 G2: 10</p>	<p><i>HAM-D 25</i> G1: rTMS G2: Sham TMS</p> <p>Endpoint score, mean (SD) At week 2 G1: 24.6 G2: 36.4</p> <p>*Adjusted Change (based on best fit slopes), mean (SEM) G1: -14.0 (3.7) G2: -0.2 (4.1) <i>P</i> < 0.05</p> <p>Responders, n 50% decrease from baseline and score <= 15 G1: 1 (10) G2: 0 <i>P</i> = 0.09 Three partial responders symptom severity returned to baseline within 1-2 weeks</p> <p><i>BDI</i> Change, mean (SD) G1: 11.4 (5) G2: 4.7 (6) <i>P</i> = 0.27</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Headache, n G1: 60 G2: 50</p> <p>Difficulty starting urination great in active group <i>P</i> = 0.03</p> <p>Remaining 21 potential side effects assessed by the SECL were not significantly different between groups after correction for multiple comparisons (data NR) • Poor memory, nausea or vomiting, constipation, drowsiness, blurred vision, increased appetite, dry mouth, decreased appetit, tremors and shakiness, nightmares, difficulty sitting still, trouble concentrating, irregular or pounding heartbeat, diarrhea, frequent need to urinate, rash, ringing in the ears, sweating, faintness or lightheadedness, poor</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval:58 • Pulses per session:800 • Total number of sessions: 10 in 10 days <p>Sham</p> <ul style="list-style-type: none"> • Paddle angled approximately 30 – 45 degrees off of scalp with bottom coil margin elevated approximately one-half cm from scalp and lucite paddle casing firmly applied against the scalp 		<p>Baseline score, mean (SD)</p> <p>G1: 37.1</p> <p>G2: 37.3</p>		<p>coordination, and muscle stiffness</p> <p>MMSE</p> <p>NR</p> <p><i>Attrition</i></p> <p>Overall, %</p> <p>15</p> <p>At end of treatment, %</p> <p>G1: 0.0</p> <p>G2: 30.0</p> <p>At end of follow-up, %</p> <p>G1: NA</p> <p>G2: NA</p> <p>Withdrawals due to efficacy, %</p> <p>G1: 0</p> <p>G2: 30</p> <p>Withdrawals due to adverse events, %</p> <p>G1: 0</p> <p>G2: 0</p> <p><i>Adherence/ compliance</i></p> <p>NR</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> George, 2010¹⁸ <small>George</small></p> <p><i>Country, setting</i> United States, outpatient</p> <p><i>Funding</i> NIMH as the Optimization of TMS for the Treatment of Depression Study</p> <p><i>Research Objective</i> To test whether daily left prefrontal rTMS safely and effectively treats major depressive disorder</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> mITT (all randomized patient who started at least 1 treatment session)</p> <p>Completer (randomized patients who were treated according to protocol and had fewer than 4 rescheduled, missed, or partially completed rTMS sessions during weeks 2 to 6)</p> <p>Fully Adherent (fewer than 2 rescheduled, missed, or partially complete sessions; must not have been taking prohibited psychiatric medications or illicit drugs; and had no other protocol violations)</p> <p><i>N</i> Randomized: 199 ITT: 190 Completers: 154 Adherent: 120</p> <p><i>Duration</i> Fixed Duration Active Treatment: 3 wks Variable Duration Active</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> Moderate level of treatment resistance as defined by the ATHF; insufficient clinical benefit to 1-4 adequate medication trials or intolerant to ≥ 3 trials; Author personal communication states, "All patients had either one failed antidepressant failure, or multiple intolerance to antidepressant medications." Not required in the current episode <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> Antidepressant medication-free outpatients; 18-70 yo; DSM-IV MDD, single or recurrent; HAM-D24 ≥ 20; Stable during 2wk medication-free lead-in; moderate level of treatment resistance as defined by the Antidepressant Treatment History Form (ATHF); insufficient clinical benefit to 1-4 adequate 	<p><i>Subgroups</i> No Subgroups</p> <p><i>Baseline n</i> mITT G1: 92 G2: 98</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: NR G2: NR</p> <p>Failed 2 or more, % G1: NR G2: NR</p> <p>Current episode failures, mean Mean, median (SD) G1: 1.62, 1 (1.37) G2: 1.41, 1 (0.97)</p> <p>Mean failed trials Mean, median (SD) G1: 3.34, 2 (2.68) G2: 3.28, 3 (2.11)</p> <p><i>Polarity, %</i> Unipolar G1: 100 G2: 100</p> <p>Bipolar I G1: 0 G2: 0</p>	<p><i>HAM-D (Insert #)</i> Yes HAM-D24 G1:rTMS G2: Sham</p> <p><i>N Analyzed</i> mITT G1: 92 G2: 98</p> <p>Observed: G1: 92 G2: 98</p> <p>Observed Endpoint: G1: 83 G2: 91</p> <p>Completers: G1: 72 G2: 82</p> <p>Fully Adherent: G1: 57 G2: 63</p> <p>Endpoint score, mean (SD) Observed G1: 21.61 (9.26) G2: 23.38 (7.43) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -4.23 to 0.10, -0.42, p = 0.06</p> <p>Change, mean (SD) Observed at 3 weeks G1: -4.65 (NR) G2: -3.13 (NR)</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p> <p>Cognitive impairment, % NR</p> <p>Dizziness, % NR</p> <p>Headache, % G1: 32 G2: 23</p> <p>Insomnia, % G1: 7.6 G2: 10</p> <p>Post op complications, % NR</p> <p>Somnolence, % G1: 5 G2: 4</p> <p>Suicidality, % Suicidality: NR</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>Treatment: 3 wks No-treatment lead-in: 2 wks HAM-D assessment performed twice weekly Acute trial terminated when patients met the stable remission criteria.</p> <p><i>Interventions</i> rTMS Sham G1: rTMS G2: Sham G1: rTMS G2: Sham G1:rTMS G2: Sham</p> <p><i>Medications Allowed</i> None (2 week washout)</p> <p><i>Strategy</i> Switch strategy</p> <p><i>Parameters</i> G1: Location: Left prefrontal cortex Frequency: 10 Hz Intensity 120% MT Pulses: 10 pulses per second for 4 seconds; 3000 persession Intertrain interval: 26 seconds Length of Session: 37.5 minutes (75 trains)</p>	<p>medication trials or intolerant to ≥ 3 trials.</p> <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Other current Axis I disorders; past failure to respond to an adequate trial of ECT; prior treatment with TMS or VNS; personal or close family history or seizure disorder; Neurologic disorder; Ferromagnetic material in body or close to head; pregnancy; taking meds known to lower seizure threshold. 	<p>Bipolar II G1: 0 G2: 0</p> <p><i>Patient Characteristics</i> <i>Age, mean yrs</i> G1: 47.7 G2: 46.5</p> <p><i>Sex, % females</i> G1: 63 G2: 51</p> <p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Not Specified, %</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: NR G2: NR</p> <p>Groups similar at baseline Yes</p> <p>HAM-D 17 Baseline score, mean (SD) G1: 26.3 (5.0) G2: 26.5 (4.8)</p> <p>BDI <i>Baseline score, mean (SD)</i></p>	<p>Responders, n mITT: G1: 14 G2: 5 p = 0.009 OR of responding to rTMS vs. Sham 4.6 (95%CI, 1.47 to 14.42) Completer: G1: 10 G2: 4 p = 0.02 Fully Adherent: Overall = 7 p = 0.14 Remitters, n No. (95%CI) mITT: G1: 13 (8.5 to 22.7) G2: 5 (2.3 to 11.4) OR (95%CI): 4.18 (1.32 to 13.24) Completers: G1: 10 (7.8 to 23.7) G2: 4 (2.0 to 11.9) OR (95%CI): 4.92 (1.29 to 18.76) Fully Adherent: G1: 6 (5.0 to 21.2) G2: 2 (1.0 to 10.8) OR (95%CI): NS Remitters by Treatment Phase Phase I Fixed(Wks 1-3) G1: 6 G2: 2 Phase I Variable (Wks 4-6)</p>	<p>Suicides: G1: 0 G2: 0</p> <p>Additional Comments Those not reported previously below: Discomfort at the stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>Fixed Active Treatment - Number of sessions: daily weekday sessions (15 sessions) Blinded treatment for improvers - Number of sessions: daily weekday sessions for up to another three weeks (total possible sessions = 30) G2: Similar coil as active treatment with a metal insert blocking the magnetic field and scalp electrodes that delivered matched somatosensory sensations.</p>			<p>Week 4 Day 2 G1: 2 G2: 0 Week 4 Day 5 G1: 3 G2: 0 Week 5 Day 2 G1: 2 G2: 3</p> <p>Other Response: ≥ 50% decrease in HAM-D score from baseline) Remission: HAM-D score of 3 or less or 2 consecutive Ham-D scores less than 10</p> <p>MADRS Yes G1: rTMS G2: Sham</p> <p>Baseline n Observed Baseline G1: 92 G2: 98 Observed End of Phase I G1: 83 G2: 91</p> <p>Baseline score, mean (SD) G1: 29.5 (6.9) G2: 29.8 (6.4)</p>	<p>Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient</p> <p><i>Neuropsychological or executive functioning</i> No</p> <p>Measures, Results NA</p> <p>Predefined No</p> <p>MMSE No</p> <p>Baseline n Baseline score, mean (SD)</p> <p>Endpoint score, mean (SD)</p> <p>Change, mean (SD)</p> <p>Other</p> <p><i>Other</i> Yes Those not reported previously below: Discomfort at the</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Endpoint score, mean (SD) Observed at 3 weeks G1: 24.59 (11.44) G2: 27.75 (9.06) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -6.10 to -0.76, -0.51, p = 0.01</p> <p>Change, mean (SD) Observed at 3 weeks G1: -4.89 (NR) G2: -2.06 (NR)</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other NA</p> <p>IDS Yes G1:rTMS G2: Sham[Q60]</p> <p>Baseline n Observed Baseline: G1: 86 G2: 94 Observed at end of Phase I: G1: 78 G2: 88</p>	<p>stimulation site (%): G1: 18 G2: 10 Worsening depression or anxiety(%): G1: 7 G2: 8 Gastrointestinal(%): G1: 7 G2: 3 Muscle Aches(%): G1: 4 G2: 4 Vertigo(%): G1: 2 G2: 2 Skin Pain(%): G1: 1 G2: 1 Facial Muscle Twitching(%): G1: 0 G2: 1 Other(%): G1: 20 G2: 15 No seizures reported Serious Adverse Events: Syncope (n): G1: 1 patient G2: 0 Paranoid Ideation: G1: 0 G2: 1 patient Adequate information Yes</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Baseline score, mean (SD) G1: 41.0 (9.3) G2: 40.1 (9.8)</p> <p>Endpoint score, mean (SD) Observed at 3 weeks G1: 32.56 (15.40) G2: 36.70 (13.91) G1: vs. G2, 95% CI, Cohen d, p-value: -10.04 to -2.62, -0.66, p = 0.001</p> <p>Change, mean (SD) Observed at 3 weeks G1: -8.42(NR) G2: -3.37 (NR)</p> <p>Responders, n NR</p> <p>Remitters, n NR</p> <p>Other NA</p> <p>CGI-S Yes G1: rTMS G2: Sham</p> <p>Baseline n Observed at baseline: G1: 90 G2: 98</p>	<p><i>Attrition</i> Overall, % All attrition calculations based on mITT 10.5%</p> <p>At end of treatment, % G1: 12 G2: 9</p> <p>At end of followup, % G1: NA G2: NA</p> <p>Withdrawals due to efficacy, % G1: NR G2: NR</p> <p>Withdrawals due to adverse events, % G1: 5.4 G2: 0</p> <p>Other</p> <p><i>Adherence/ compliance</i> Adherence Fully Adherent n= 120 G1: n = 57 G2: n = 63</p>

Evidence Table 35. KQ 4. Adherence: Tier 2 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>Observed at end of Phase I: G1: 82 G2: 90</p> <p>Baseline score, mean (SD) G1: 4.62 (0.70) G2: 4.63 (0.69)</p> <p>Endpoint score, mean (SD) Observed at 3 weeks G1: 3.96 (1.14) G2: 4.30 (0.87) G1: vs. G2, 95% CI Effect Estimate, Cohen d, p-value: -0.68 to -0.09, -0.55, p = 0.01</p> <p>Change, mean (SD) Observed at 3 weeks G1: -0.66 (NR) G2: -0.33(NR)</p> <p>Other NA</p>	

Evidence Table 36. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD only)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Moore et al., 1997⁴³</p> <p><i>Country, setting</i> Scotland, University clinic, outpatients</p> <p><i>Funding</i> Scottish Office, Home and Health Department</p> <p><i>Research Objective</i> To compare CBT to additional meds in treatment of depression non-responsive to medication during acute phase of study (results of Phase 1 reported elsewhere).</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers confirmed with ITT</p> <p><i>N</i> 13</p> <p><i>Duration</i> 12 months</p> <p><i>Interventions</i> G1: Medication G2: Cognitive Therapy</p> <p><i>Medication Allowed</i> G1: Continued AD assigned in acute phase OR initiated another AD txt G2: Discontinued AD</p> <p><i>Strategy</i> Mixed-between group differences</p> <p><i>Parameters</i> • Medication dose within recognized therapeutic threshold • Psychotherapy • Type of therapy: Cognitive Therapy • Method: NR</p>	<p><i>TRD definition</i> • Failure to respond to AD medication during 16 wk acute txt phase • Failure required to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • HAM-D > 14</p> <p><i>Exclusion criteria</i> NA</p>	<p><i>Baseline N</i> G1: 7 G2: 6</p> <p><i>Treatment Failure</i> Current episode failures, mean G1: NR</p> <p>Mean failed trials G1: NR</p> <p><i>Polarity, %</i> Unipolar Overall: 100</p> <p><i>Age, mean yrs</i> Overall: 38</p> <p><i>Sex, % females</i> Overall: 62</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 18.6 (3.3) G2: 18.3 (3.9)</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 30.6 (5.1) G2: 37.8 (5.1)</p>	<p><i>Analyzed, n</i> G1: 4 G2: 5</p> <p><i>HAM-D 17</i> Endpoint score, mean (SD) 4 mos G1: 11.0 (2.3) G2: 19.8 (5.6)</p> <p>8 mos G1: 6.6 (7.3) G2: 17.5 (1.9)</p> <p>12 mos G1: 5.0 (5.7) G2: 14.3 (4.0)</p> <p>Completers, group by time, <i>P</i> < 0.01 ITT (LOCF), group by time, <i>P</i> < 0.01</p> <p>Change, mean (SD) 4 month G1: -7.6 G2: +1.5</p> <p>Partial responders, n Defined as HAM-D ≤ 14 G1: 5 G2: 2 <i>P</i> = 0.17</p> <p>Full responders, n Defined as HAM-D ≤ 6 G1: 3</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 31%</p> <p>At end of treatment, % G1: 43 G2: 17</p> <p>At end of follow-up, % G1: 43 G2: 17</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 36. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD only) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Number of sessions/week: min. 3/wk for 4wks and then 2/wk for 4wks and 1/wk for 4wks • Total number of sessions: NR 			<p>G2: 0 P = NR</p> <p><i>BDI</i> Endpoint score, mean (SD)</p> <p>4 mos. G1: 22.2 (5.9) G2: 41.5 (5.8)</p> <p>8 mos. G1: 9.2 (8.3) G2: 34.3 (12.0)</p> <p>12 mos. G1: 10.8 (12.2) G2: 35.8 (12.6) Group by time, P = 0.05 ITT (LOCF), group by time, P < 0.05</p> <p>Change, mean (SD) At 4 months G1: -8.4 G2: +3.7</p> <p>Partial responders, n Defined as BDI ≤ 16 G1: 4 G2: 0 P < 0.05</p> <p>Full responders, n Defined as BDI ≤ 9 G1: 3 G2: 0 P = NR</p>	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Harley, 2008³⁶</p> <p><i>Country, setting</i> United States, university clinics, outpatient psychiatric</p> <p><i>Funding</i> Kaplan Fellowship Award Grant through Harvard Medical School</p> <p><i>Research Objective</i> To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 24</p> <p><i>Duration</i> Primary outcome after 16 weeks of active txt Follow-up: 6 months</p> <p><i>Interventions</i> G1: Dialectical Behavior Therapy(DBT)-based skills training G2: Wait-list Control</p> <p><i>Medications Allowed</i> Patients continued antidepressant therapy</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1</p>	<p><i>TRD definition</i> • 1+ failed medications (6+ weeks at “standard effective dose”) • Not required or not specified to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabilized on an adequate dose of antidepressant medication before entering study.</p> <p><i>Exclusion criteria</i> • Borderline personality disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.</p>	<p><i>Baseline N</i> G1: 13 G2: 11</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> MDD</p> <p><i>Overall:</i> 100</p> <p><i>Age, mean yrs</i> Overall: 41.8</p> <p><i>Sex, % females</i> Overall: 75</p> <p><i>Race, % white</i> Overall: 83</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) P = NS</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) P = NS</p>	<p><i>HAM-D 17</i> Analyzed n G1: 10 G2: 9</p> <p>Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23)</p> <p>Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78</p> <p><i>P < 0.05</i> Remitters, n Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) P = NR</p> <p><i>BDI</i> Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30)</p>	<p><i>Quality of Life</i> <i>Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT)</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24)</p> <p>Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69)</p> <p>Change, mean (SD) G1: -1.3 G2: -0.33 P = NS</p> <p><i>Social Adjustment Scale-Self-Report (SAS-SR) work subscale</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)</p>

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> Total number of sessions:16 G2: Wait list 	<ul style="list-style-type: none"> Active suicidality requiring more intensive levels of care Severe or unstable medical conditions Previous or current CBT experience. 		Change, mean (SD) G1: -12.80 G2: -1.55 P < 0.01	Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66) Change, mean (SD) G1: -16.80 G2: 0.34 P < 0.05 <i>Adverse Events</i> NR <i>MMSE</i> NR <i>Attrition</i> Overall, %: 21 At end of treatment, % G1:23 G2:18 At end of follow-up, % G1:20 G2: NR Withdrawals due to efficacy, % G1: 8 G2: 0 Withdrawals due to adverse events, % 0

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem prevented second from continuing.</p> <p><i>Adherence/ compliance</i> Compliance Participants completed a weekly check-in form asking about medication compliance over preceding month. 19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had forgotten a medication dose between 1 to 4 times in previous month.</p>

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Paykel, 1999³⁸ Scott, 2000⁵⁹</p> <p>Note: #2223 and #2219 are companion studies, data from #2223 were abstracted in to form for #2219.</p> <p><i>Country, setting</i> UK, outpatient</p> <p><i>Funding</i> Medical Research Council, London, England and a grant from Oxford and Anglia Region</p> <p><i>Research Objective</i> To compare cognitive therapy combined with clinical management to clinical management alone for patients with residual depressive symptoms who continued to receive maintenance treatment with antidepressants.</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 158</p> <p><i>Duration</i> Treatment period = 20 weeks; 48 wks - follow-up: Subjects were assessed every 4 to 20 wks and every 8 wks thereafter at baseline, 8 wks, 20 wks, and 68 wks.</p> <p><i>Interventions</i> G1: Clinical management Only G2: CT plus Clinical Management</p> <p><i>Medications allowed</i> Continued on current medications with dose adjustments allowed</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> Psychotherapy: • Type of therapy: Cognitive Therapy • Method: Individual</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • residual symptoms reaching at least 8 on the 17-item Hamilton Depression Rating Scale (HDRS)18 and 9 on the Beck Depression Inventory (BDI) and taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least the previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, • Residual symptoms had lasted 2 to 18 months. • Failure required to be in the current episode <p><i>Tier 2 Inclusion criteria</i></p> <ul style="list-style-type: none"> • Unipolar depression, • aged 21 to 65 years, • satisfying DSM-III-R17 criteria for major depression within last 18 months but not in last 2 months, and 	<p><i>Treatment Failure</i> Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar 100%</p> <p><i>Age, mean yrs</i> G1: 43.2 (11.2) G2: 43.5 (9.8)</p> <p><i>Sex, % females</i> G1: 53% G2: 46%</p> <p><i>HAM-D 17</i> Baseline n G1: 78 G2: 80</p> <p>Baseline score, mean (SD) G1: 12.2 (2.9) G2: 12.1 (2.7)</p> <p>BDI Baseline score, mean (SD) G1: 22.3 (8.0) G2: 21.9 (7.7)</p>	<p>HAM-D 17 G1: Clinical Management only G2: CT plus Clinical Management</p> <p>Endpoint score, mean (SD) At week 20 G1: 9.40 (5.2) G2 (5.2)</p> <p>Follow-up at 44 weeks G1: 8.7 (5.3) G2: 7.6 (4.7)</p> <p>Follow-up at 68 weeks G1: 7.2 (4.7) G2: 7.2 (5.3)</p> <p>Change, mean (SD) At week 20 G1: -2.8 G2: -3.4 P = NS</p> <p>Follow-up at 44 weeks G1: - 3.0 G2: -4.5</p> <p>Follow-up at 68 weeks G1: -5.0 G2: -4.9</p> <p>Responders, n NR</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> NR</p> <p><i>Attrition</i> Overall, % 20% did not adhere to protocol through to study end or relapse point</p> <p>At end of treatment, % G1: 4 G2: 14</p> <p>At end of follow-up, % G1: 12 G2: 10</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % NR</p> <p><i>Adherence/ compliance</i> Adherence, n(%) G1: 61 (76%) G2: 66 subjects (85) [Control]</p>

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Number of sessions/week: 1.25/wk • Total number of sessions: 16 	<ul style="list-style-type: none"> • Had to be taking a tricyclic antidepressant, serotonin reuptake inhibitor, atypical antidepressant, or monoamine oxidase inhibitor for at least previous 8 weeks, with 4 or more weeks at a daily dose at least equivalent to 125 mg of amitriptyline, and higher levels unless there were definite current adverse effects or patient refusal to increase dose. <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • A history of bipolar disorder, cyclothymia, schizoaffective disorder, definite • Intervention or alcohol dependence, persistent antisocial behavior or repeated self-harm, • DSM-III-R dysthymia with onset before age 20 years, • borderline personality, learning disability (estimated IQ,70), • organic brain damage, 		<p>Remitters, n (%) HAM-D<8 At week 20 G1: 10 (13) G2: 19 (24) Hazard Ratio for remission from intention to treat analysis: 2.42 (95% CI, (1.08, 5.45))</p> <p>BDI Endpoint score, mean (SD) At 20 weeks G1: 16.1 (10.0), G2: 13.8 (9.6),</p> <p>Follow-up at 44 weeks G1: 17.3 (11.6) G2: 12.3 (9.3)</p> <p>Follow-up at 68 weeks G1: 14.3 (10.9) G2: 13.5 (11.7)</p> <p>Change, mean (SD) At week 20 G1: -6.24 G2: -8.44</p> <p>Responders, n NR</p> <p>Remitters, n BDI <9 At week 20 G1: 10 (13%) G2: 19 (24.4%)</p>	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<ul style="list-style-type: none"> • any other primary Axis I disorder at time of index illness. • Also excluded were patients currently receiving formal psychotherapy or those who had previously received CT for more than 5 sessions. 		<p>Relapse n(%):</p> <p>At week 20: G1: 18 (23) G2: 10 (13)</p> <p>At week 44 G1: 40 (51) G2: 24 (30)</p> <p>At week 68 G1: 47 (60) G2: 29 (36)</p> <p>Hazard ratio for relapse = 0.54 (0.32-0.93) in favor of CT</p> <p>Actuarial Cumulative relapse rates at all time points for group 1: Awk20 = 18%, FUwk44 = 40%, FUwk68 = 47%;</p> <p>Actuarial Cumulative relapse rates at all time points for group 2: Awk20 = 10%, FUwk44 = 24%, FUwk68 = 29%;adjusted hazard ratio for relapse = 0.51, 95% CI, (0.32, 0.93).</p> <p>Over 17 months,relapse rate was reduced from 47% among those who continued to be treated with antidepressants without CT to 29% among those who also received CT. #2219:</p> <p>Relapse was defined as: (1) meeting DSM-III criteria for major depressive disorder for</p>	

Evidence Table 37. KQ 4. Adherence: Tier 2 (CBT vs. usual care—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				<p>a minimum of 1 month, and meeting severity criteria for major depression and score 17 or more onHAM-D 17 at 2 consecutive face-to-face assessments at least 1 week apart; (2) persistent residual symptoms duringfollow-up phase between 2 successive ratings 2 months apart, reaching a score onHAM-D 17 of at least 13 on both occasions and a level of distress or dysfunction for whichthe withholding of additional active treatment was no longer justified</p>	

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Hansen, 2010⁶ Hansen</p> <p><i>Country, setting</i> Denmark University Hospital Inpatient Psychiatric</p> <p><i>Funding</i> Danish Council for Medical Research; Einar Geert-Jorgensen and Wife Ellen Geert-Jorgensen Research Foundation; Boutcher Worzner and wife Inger Worzner grant; the Aarhus University Foundation for Research in Mental Disease; the Foundation of Psychiatric Research</p> <p><i>Research Objective</i> To compare the antidepressant efficacy and adverse effects of right prefrontal low-frequency rTMS with that of ECT.</p> <p><i>Quality Rating</i> Fair - KQ1 KQ4?</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT PP</p> <p><i>N</i> 60</p> <p><i>Duration</i> Active treatment: 3 wks HAMD and UKU assessed at baseline and weekly intervals w/in 24 hrs of treatment Follow-up treatment: 7 wks (total duration) HAMD and UKU assessed at wk 5 and wk 7</p> <p><i>Interventions</i> ECT rTMS G1: rTMS G2: ECT</p> <p><i>Medications Allowed</i> Continued current antidepressant medication; discontinued antiepileptics prescribed as mood stabilizers, benzodiazepines</p>	<p><i>TRD definition</i> • Patients referred for ECT</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • 18-80 yo; HAMD-17 total score of ≥ 20 and/or subscale score of ≥ 9; right-handed; ICD-10 diagnosis of moderate to severe depression; DSM-IV diagnosis of MDD; unipolar or bipolar</p> <p><i>Exclusion criteria</i> • Organic brain damage; personal/family history of epileptic seizures, metallic objects in the chest or brain as a result of surgery; cardiac pacemakers; somatic diseases associated w/ brain dysfunction; pregnancy; use of coercive measures; suicidal risk of severe degree; severe agitation; delirium; alcohol or drug dependence.</p>	<p><i>Subgroups</i> No Subgroups</p> <p><i>Baseline n</i> G1: 30 G2: 30</p> <p><i>Treatment Failure</i> Failed 1 or more, % G1: NR G2: NR</p> <p>Failed 2 or more, % G1: NR G2: NR</p> <p>Current episode failures, mean G1: NR G2: NR</p> <p>Mean failed trials G1: NR G2: NR</p> <p><i>Polarity, %</i> Unipolar G1: 86.7 G2: 86.7</p> <p>Bipolar I G1: 13.3 G2: 13.3</p> <p>Bipolar II G1: NR G2: NR</p>	<p><i>HAM-D (Insert #)</i> Yes HAM-D17 G1: rTMS G2: ECT</p> <p>Endpoint score, mean (SD) Week 3 G1: NR Baseline - wk3 reduction, p <0.001 G2: NR Baseline - wk3 reduction, p <0.001 Week 3-7 G1: NR wk3 - wk7 reduction, p <0.001 G2: NR wk3 - wk7 reduction, p = 0.78 Week 7 G1: NR Baseline - wk 7 reduction, p < 0.001 G2: NR Baseline - wk 7 reduction, p < 0.001 Change, mean (SD) G1: NR G2: NR</p> <p>Responders, n Response Rate Difference Week 3, Rate (95% CI):</p>	<p><i>Quality of Life</i> No</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p> <p>Cognitive impairment, % G1: 0 G2: 0</p> <p>Dizziness, % NR</p> <p>Headache, % NR</p> <p>Insomnia, % NR</p> <p>Post op complications, % NR</p> <p>Somnolence, % Significantly > decline in fatigue score in the ECT group (score NR)</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>tapered off, low dose zopiclone or zopidem if needed for sleep</p> <p><i>Strategy</i> Augment or add-on strategy</p> <p><i>Parameters</i> G1: Location: Right DLPFC Frequency: 1 Hz Intensity: 110% MT Trains: 2 60s trains Intertrain interval: 180 s Number of session: 15 total (1 per week day for 3 weeks) G2: Location: Unilaterally over the right hemisphere Intensity: Recorded seizure duration ≥ 25 seconds; If between 15-25 seconds next treatment carried out with 50% higher stimulus intensity; If < 15 seconds then followed by restimulation. Number of session: 9 total (3 sessions weekly)</p>		<p><i>Patient Characteristics</i></p> <p><i>Age, mean yrs</i> Median (range) G1: 46 (14-38) G2: 52 (29-79) p = 0.16</p> <p><i>Sex, % females</i> G1: 76.7 G2: 63.3</p> <p><i>Race, % white</i> G1: NR G2: NR</p> <p><i>Not Specified, %</i> G1: NR G2: NR</p> <p><i>Right handed, %</i> G1: 100 G2: 100</p> <p><i>Groups similar at baseline</i> Yes</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) Median (Range): G1: 24 (14-38) G2: 24 (16-34) G1: vs. G2: p = 0.68</p>	<p>G1: 0.20 (0.08-0.39) G2: 0.57 (0.37-0.75) G1: vs. G2 rate difference: 0.37 (0.14-0.59), p = 0.003 Week 7, Rate (95%CI): G1: 0.43 (0.25-0.63) G2: 0.60 (0.41-0.77) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200</p> <p>Remitters, n Remission Rate Difference Week 3 Rate (95% CI): G1: 0.27 (0.12 - 0.46) G2: 0.53 (0.34 - 0.72) G1: vs. G2 rate difference: 0.26 (0.03 - 0.51), p = 0.035 Week 7 Rate (95% CI): G1: 0.40 (0.23 - 0.59) G2: 0.57 (0.37 - 0.75) G1: vs. G2 rate difference: 0.17 (-0.08, 0.42), p = 0.200</p> <p>Other Remission: HAM-D-17 ≤ 12</p>	<p>Suicidality, % NR</p> <p>Additional Comments NR "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale.</p> <p><i>Neuropsychological or executive functioning</i> Yes</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
				Response: ≥ 50% reduction in HAMD-17	Measures, Results Logical Memory – Immediate recall Baseline, Mean (SD): G1: 10.8 (4.4) G2: 10.0 (5.1) After Treatment G1: 8.8 (3.8) G2: 9.6 (5.1) Logical Memory – Delayed recall Baseline, Mean (SD): G1: 7.6 (5.4) G2: 7.46 (5.5) After Treatment G1: 7.2 (3.7) G2: 6.8 (5.8) Verbal Learning – Total Baseline, Mean (SD) G1: 8.2 (1.7) G2: 8.4 (2.1) After Treatment G1: 8.1 (2.0) G2: 7.9 (1.5) Verbal Learning – delayed recall Baseline, Mean (SD) G1: 5.9 (2.3) G2: 5.5 (2.0) After Treatment G1: 6.0 (2.6) G2: 4.8 (3.1) Rey Complex Figure – copy Baseline, Mean (SD) G1: 32.9 (4.2) G2: 29.7 (7.4)

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					After Treatment G1: 33.6 (2.2) G2: 29.2 (6.8) Rey Complex Figure – delayed recall Baseline, Mean (SD) G1: 16.0 (6.2) G2: 13.9 (7.2) After Treatment G1: 25.6 (7.4) G2: 13.1 (9.4) G1: vs. G2, p <0.01 Within groups, p <0.01 Trail-Making Test A Baseline, Mean (SD) G1: 65.7 (35.5) G2: 64.7 (23.5) After Treatment G1: 60.6 (39.4) G2: 65.9 (34.0) Trail-Making Test B Baseline, Mean (SD) G1: 147.8 (64.4) G2: 131.3 (50.1) After Treatment G1: 131.0 (68.0) G2: 107.8 (36.0) SDMT Baseline, Mean (SD) G1: 29.9 (12.0) G2: 29.3 (13.7) After Treatment G1: 34.0 (12.6) G2: 31.1 (14.0) Verbal Fluency – letter S

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Baseline, Mean (S) G1: 10.4 (3.8) G2: 11.6 (7.3) After Treatment G1: 12.9 (5.6) G2: 10.3 (6.1) Verbal Fluency – animals Baseline, Mean (SD) G1: 18.4 (6.3) G2: 16.3 (4.5) After Treatment G1: 19.8 (6.2) G2: 14.11 (3.1) G1: vs. G2, p < 0.05</p> <p><i>Other</i> Yes "Both treatment forms were generally well tolerated. No serious adverse effects were reported. For 5 patients, rTMS was associated with severe local discomfort or pain, and 4 of them dropped out for that reason. The rest of the rTMS group experienced no or only slight inconvenience. Both groups revealed declining scores during the treatment period. The statistical analyses controlled for several essential variables(data</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>not shown)...None of the 2 methods were associated with cognitive adverse effects or serious adverse effects on the UKU rating scale.</p> <p>Adequate information Yes</p> <p><i>Attrition</i> Overall, % 30</p> <p>At end of treatment, % G1: 33.3 G2: 26.7</p> <p>At end of followup, % G1: NR G2: NR</p> <p>Withdrawals due to efficacy, % G1: NR G2: NR</p> <p>Withdrawals due to adverse events, % G1: NR G2: NR</p> <p>Other Withdrawal due to Discomfort at the stimulus site, % (n): G1: 16.7 (5) G2: 0 (0)</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					Withdrawal due to serious deterioration, % (n): G1: 10 (3) G2: 3 (1) Withdrawal due to somatic disease, % (n): G1: 3 (1) G2: 0 (0) Withdrawal due to Comotio cerebri, % (n): G1: 0 (0) G2: 3 (1) Withdrawal for unknown reasons, % (n): G1: 0 (0) G2: 3 (1) <i>Adherence/ compliance</i> None reported
<p><i>Author, Year</i> McLoughlin et al., 2007⁷ Eranti et al., 2007⁸ Knapp et al., 2008⁹ <i>Country, setting</i> UK, South London and Maudsley NHS Trust and Pembury Hospital inInvicta Mental Health Trust in Kent, 65.2% were inpatients <i>Funding</i> National Health Service Research and Development, National Coordinating Centre for</p>	<p><i>Study design</i> RCT- pragmatic and single blinded (raters) <i>Type of analysis</i> m-ITT <i>N</i> 46 <i>Duration</i> Primary endpoint at 3 weeks for rTMS and at clinicians discretion for ECT, additional follow-up at 6 months</p>	<p><i>TRD definition</i> • All patients referred for ECT: • No failure required <i>Tier 3</i> <i>Inclusion criteria</i> • Right handed patients • more than 18 years old • referred for ECT due to major depressive episode <i>Exclusion criteria</i> • Inability to have rTMS because of metallic</p>	<p><i>Treatment Failure</i> Mean failed trials G1: 2.5 (1.4) G2: 2.4 (1.0) Polarity, % MDD G1: 91.67 G2: 90.91 Bipolar G1: 8.33% G2: 9.09 % <i>Age, mean yrs</i> G1: 63.6 G2: 68.3</p>	<p><i>HAM-D 17</i> Analyzed n G1: 22 G2: 23 Endpoint score, mean (SD) End of treatment G1: 10.7 G2: 18.5 P = 0.002, effect size of 1.44 Follow-up at 6 months G1: NR G2: NR P = 0.93</p>	<p><i>Quality of Life</i> SF-36 mental health component score Baseline n G1: 24 G2: 22 Baseline score, mean (SD) G1: 48.9 (12.6) G2: 42.7 (7.5) Other: QALYs</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p>Health Technology Assessment (NCCHTA) (98/11/04); by Guy's and St. Thomas's Charitable Foundation (R001126); and by a 2003 Ritter Independent Investigator Award from National Alliance for Research on Schizophrenia and Depression.</p> <p><i>Research Objective</i> To assess clinical effectiveness of rTMS vs. ECT for treating major depressive episodes in patients referred for ECT</p> <p><i>Quality Rating</i> Good</p>	<p><i>Interventions</i> G1: ECT G2: rTMS</p> <p><i>Medication Allowed</i> Patients continued their usual medical care and stable psychotropic medications were allowed (i.e. SSRIS, TCAs, Venlafaxine, Mirtazapine, Lithium, Anticonvulsant mood stabilizers, Benzodiazepines, Antipsychotics, Zopiclone, L-Tryptophan)</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz): 10 • Motor threshold (%): 110 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 55 • Pulses per session: 1000 • Total number of sessions: 15 	<ul style="list-style-type: none"> • implants or foreign bodies • History of seizures • Substance misuse in previous 6 months • Being medically unfit for general anesthesia or ECT: • ECT or rTMS in previous 6 months, • Dementia or other axis I diagnosis • Inability or refusal to provide informed consent. 	<p><i>Sex, % females</i> G1: 67.7 G2: 72.7</p> <p><i>Right handed, %</i> Overall: 100%</p> <p><i>HAM-D 17</i> Baseline n G1: 22 G2: 24</p> <p>Baseline score, mean (SD) G1: 24.8 (5.0) G2: 23.9 (7.0)</p> <p><i>BDI:</i> Baseline score, mean (SD) G1: 36 (8.7) G2: 37.8 (10.5)</p>	<p>Change, mean (SD) End of treatment G1: -14.1 G2: -5.4 <i>P</i> = 0.017</p> <p>Responders, n End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p>Remitters, n HAM-D ≤ 8 End of treatment G1: 13 (59.1%) G2: 4 (17.4%) <i>P</i> = 0.005</p> <p>Follow-up at 6 months* G1: 6 (27.4%) G2: 2 (8.7%)</p> <p>*only 12 ECT remitters followed after End of txt</p> <p><i>BDI</i> Endpoint score, mean (SD) NR <i>P</i> = 0.01 effect size=0.9</p> <p>Change, mean (SD) NR Group x time, <i>P</i> = 0.25</p>	<p>Six month QALY gain, mean (SD) G1: 0.0300 (0.053) G2: 0.0297 (0.056)</p> <p>(QALYs were derived using SF-36 data). At six month follow-up, service use data were collected on 28 pts (10-ECT and 18-rTMS). Patients responded much better to ECT than to rTMS by the end of the allocated treatment course.</p> <p>The differential QALY gain of treatment with rTMS over ECT was 0.0003 (<i>p</i> = 0.987). This suggests that treatment by rTMS does not provide any additional gains in quality of life over ECT over a 6-month period. The lack of a statistically significant difference in QALY gain between the two groups may reflect lack of difference in HRSD scores between groups at 6 months.</p> <p><i>Adverse Events</i> NR</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>ECT:</p> <ul style="list-style-type: none"> • % receiving bilateral: 82 • Intensity: 1.5 × ST for bilateral frontotemporal ECT and 2.5 × ST for right unilateral ECT • Number of sessions (range, mean, SD): range = 2-10, mean = 6.3, SD = 2.5 			<p>Responders, n NR</p> <p>Remitters, n NR</p>	<p><i>Neuropsychological or executive functioning</i></p> <p>Predefined</p> <p>CAMCOG Attention and orientation subscale (max = 17): ECT baseline 12.8 (3.2), end of treatment 13.9 (3.6), 6mos 13.9 (3.5) rTMS baseline 14.7 (3.0) end of treatment 13.5 (3.3) FU6mos 13.4 (3.8), <i>P</i> = 0.004</p> <p>No significant differences for rest of CAMCOG subscales (verbal fluency, anterograde memory, and retrograde memory)</p> <p>MMSE</p> <p>Baseline score, mean (SD) G1: 24.3 (3.6) G2: 25.7 (3.9)</p> <p>Score at 6 months, mean (SD) G1: 25.4 (5.3) G2: 24.7 (4.8)</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Endpoint score, mean (SD) G1: 25.6 (3.9) G2: 24.4 (5.3)</p> <p>Change, mean (SD): G1: 1.3 G2: -1.3 <i>P</i> < 0.08</p> <p>No significant differences on the Columbia ECT Subjective Side Effects Schedule for self-reported cognitive side effects.</p> <p>Attrition Overall to end of treatment 6/46, at 6 months 9/46</p> <p>At end of treatment, % G1: 6/24 G2: 0</p> <p>At end of follow-up, % NR</p> <p>Withdrawals due to efficacy, % G1: 5/24 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> O'Connor, 2003⁶⁴</p> <p><i>Country, setting</i> United States, University Hospital, inpatient vs. outpatient population not clearly reported</p> <p><i>Funding</i> NIH/NIMH and a NARSAD grant</p> <p><i>Research Objective</i> Two procedures for treating major depressive disorder were compared with regard to their respective effects on mood and cognition</p> <p><i>Quality Rating</i> Poor</p>	<p><i>Study design</i> Observational</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 28</p> <p><i>Duration</i> • Primary outcome at end of treatment (ECT applied for 2 to 4 weeks and rTMS a period of 2 weeks). • Patients assessed for follow-up 2 weeks post txt</p> <p><i>Medications allowed</i> rTMS patients completed a washout of all psychotropic medications while ECT continued all medications</p> <p><i>Strategy</i> Switch strategy for rTMS and augment or add-on strategy for ECT group</p> <p><i>Interventions</i> G1: ECT G2: rTMS</p>	<p><i>TRD definition</i> • Patients referred for ECT • AD failures not required</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • Met criteria for MDD • HRSD > 18</p> <p><i>Exclusion criteria</i> • Psychosis, acute suicidality, other current Axis I diagnoses in DSM IV • known CNS pathology, pacemakers, electronic or metallic implants, severe cardiac pathology • personal or first degree family history of a seizure disorder • inability to give informed consent</p>	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> 100% MDD</p> <p><i>Age, mean yrs</i> G1: 48.4+/- 12.0 G2: 51.2 +/- 12.2</p> <p><i>HAM-D</i> Baseline n Completers G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 38.07 (8.1) G2: 29.3 (4.9) <i>P</i> = 0.001</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 10.92 (2.49) G2: 10.42 (3.0)</p>	<p><i>HAM-D</i> Endpoint score, mean (SD) End of treatment G1: 15.3 (11.7) G2: 25.6 (7.7) Follow-up 2 weeks G1: 20.4 (9.5) G2: 24.8 (9.5)</p> <p>Change, mean (SD) End of treatment G1: -23.7 G2: -3.73 Group x time <i>P</i> < 0.01</p> <p>Responders, n G1: NR G2: 0</p> <p>Remitters, n G1: NR G2: 100%</p> <p><i>Other</i> Validated measure Yes</p> <p><i>Wechsler Memory Scale-III (WMS-III)-Letter Number Sequencing subtest</i> Endpoint score, mean (SD) G1: 9.23 (1.83) G2: 10.71 (3.83)</p>	<p><i>Adherence/ compliance</i> NR</p> <p><i>Quality of Life</i></p> <p><i>Adverse Events</i> NR</p> <p><i>Neuropsychological or executive functioning</i> Rey Auditory Verbal Learning Test-RAVLT (15 item word list to test new learning)</p> <p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 43.78 (11.07) G2: 43.71 (12.09)</p> <p>Endpoint score, mean (SD) G1: 29.14 (7.93) G2: 43.00 (10.00)</p> <p>Change, mean (SD) G1: 46.92 (10.80) Difference between baseline acquisition and performance on acquisition task during 2-wk f/u session was not significant: <i>P</i> > 0.05</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p><i>Parameters</i></p> <p>ECT</p> <ul style="list-style-type: none"> • % receiving bilateral:0 • Intensity: 2.5 times seizure threshold • Number of sessions (range, mean, SD): 6-12, <p>rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):10 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 8 • Inter-train interval: 24 • Pulses per session: 1600 • Total number of sessions:5/wk over 2wks 			<p>Change, mean (SD) At two weeks ECT scores on LN based on completers per protocol (n=13). ECT pts did not demonstrate a significant change in LN performance compared directly with2 week follow-up results ($P > 0.05$)</p> <p>No significant interaction between treatment sessions and groups with respect to LN ($P > 0.05$)</p>	<p>G2: 44.07 (10.43)</p> <p>RAVLT, Acquisition, mean (SD)</p> <p>Baseline: ECT 43.78 (11.07) vs. rTMS 43.71 (12.09).</p> <p>End of treatment: ECT 29.14 (7.93) vs. rTMS 43.00 (10.09) $P < 0.01$.</p> <p>Two weeks later: ECT 46.92 (10.80) vs. rTMS 44.07 (10.43) $P > 0.05$.</p> <p>RAVLT, Retention,(15-item word list after a 20-minute delay interval), mean (SD)</p> <p>Baseline ECT 8.07 (4.49) words vs. rTMS 9.76 (3.08)</p> <p>End of treatment ECT 2.14 (1.99) vs. rTMS 8.23 (2.80)</p> <p>Two weeks later, ECT 8.92 (4.14) vs. rTMS 8.31 (4.07).</p> <p>Transient News Events Test (TNET-measure of retrograde memory)</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Baseline n G1: 14 G2: 14</p> <p>Baseline score, mean (SD) G1: 64.30 (19.40) G2: 55.62 (18.12)</p> <p>Endpoint score, mean (SD) G1: 39.10 (13.21) G2: 57.81 (18.33)</p> <p>Change, mean (SD) G1: 59.20 (20.67) G2: 61.54 (19.12)</p> <p>Other Main-effect-of-group ($P > 0.05$). There was evidence of a significant interaction b/t txt grp and txt session: $P < 0.001$.</p> <p>Cognitive function/memory impairment reported as primary outcome measures.</p> <p><i>MMSE</i> NR</p> <p><i>Attrition</i> Overall, % No attrition</p>

Evidence Table 38. KQ 4. Adherence: Tier 3 (ECT vs. rTMS—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					At end of treatment, % NR At end of follow-up, % NR Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 <i>Adherence/ compliance</i> NR

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Bortolomasi et al., 2006³⁴</p> <p><i>Country, setting</i> Italy, single center, inpatient vs. outpatient NR</p> <p><i>Funding</i> Not reported</p> <p><i>Research Objective</i> To investigate outcome of depressed patients treated for 1 month with high frequency rTMS on left frontal lobe at long time periods</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Cannot tell, all reported patients included in analysis</p> <p><i>N</i> 19</p> <p><i>Duration</i> Active: 5* days Follow-up: 1, 4 and 12 weeks, co -primary endpoints HAM-D and BDI *duration of txt is unclear in article</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications allowed</i> Patients continued their (failed) ADs and no medications changes were allowed (5.3% were not taking medications at study entry)</p> <p><i>Strategy</i> Augmentation Allowed to continue on failed SSRIs (63.2%)</p>	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • Drug resistance (not defined) • Not required or not specified to be in current episode <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • DSM-IV clinical criteria for major depression, right-handed, normal neurological examinations <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Hx of brain trauma or seizure disorder • Pacemakers, mobile metal implants or implanted medication pumps 	<p><i>Treatment Failure</i></p> <p>Mean failed trials NR</p> <p><i>Polarity, %</i> Unipolar G1: 83.3 G2: 85.7</p> <p>Bipolar G1: 16.7 G2: 14.3</p> <p><i>Age, mean yrs</i> G1: range 45-56 G2: range 44-53 Overall: 55.6</p> <p><i>Sex, % females</i> G1: 58 G2: 57</p> <p><i>Race, % white</i> NR</p> <p><i>Right handed, %</i> Overall: 100</p> <p>Groups similar at baseline Yes</p>	<p><i>HAM-D 24</i></p> <p>Endpoint score, mean (SD) At week 1 G1: 11.33 G2: 18.29</p> <p>At week 4 G1: 11.42 G2: 19.14</p> <p>At week 12 NR</p> <p>Change, mean (SD) At week 1 G1: -13.84 G2: NR <i>P</i> = NR, significant Group x time at wk 2 and 4, <i>P</i> < 0.05</p> <p>At week 4 G1: -13.75 G2: NR At week 12 NR</p> <p>IG1: rTMS G2: Sham</p> <p>Baseline n G1: 12 G2: 7</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> No adverse effects were reported in either group, except for mild cephalgia by three patients treated with anti-inflammatory drugs</p> <p>Headache, % 3 patients reported mild headaches after treatment All rTMS patients referred to marked drowsiness for several hours immediately following. Six patients referred to subjective improvement of sleep after first stimulation session. Patients treated with sham condition did not report any symptoms related to drowsiness or sleep. 3 patients reported mild headaches after treatment</p> <p><i>Attrition</i></p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>and TCAs (26.3%), No meds (5.3%)</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Frequency (Hz):20 • Motor threshold (%): 90 • Number of trains: 20 • Length of train (seconds): 2 • Inter-train interval: 60 • Pulses per session: 800 • Total number of sessions: 5/wk • Circular coil <p>Sham</p> <ul style="list-style-type: none"> • Stimulation coil was placed perpendicular to the scalp surface without direct contact. Coil position was fixed for all TMS sessions, and stimulation at this site evoked minimal motor activity 		<p><i>Tier</i></p> <p><i>HAM-D 24</i> Baseline n G1: 12 G2: 7</p> <p>Baseline score, mean (SD) G1: 25.17 G2: NR</p>	<p>Baseline score, mean (SD) G1: 25.42 G2: NR</p> <p>Endpoint score, mean (SD) At week 1 G1: 12.25 G2: 22.43 At week 4 G1: 11.67 G2: 24.57</p> <p>Change, mean (SD) At week 1 G1: 13.17 G2: NR At week 4 G1: 13.75 G2: NR</p>	

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> George et al., 1997³⁵</p> <p><i>Country, setting</i> USA, outpatient setting</p> <p><i>Funding</i> NARSAD, Ted and Vada Stanley Foundation</p> <p><i>Research Objective</i> To test hypothesis: daily left prefrontal rTMS has antidepressant effects</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT, crossover</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 12</p> <p><i>Duration</i> 4 wk (2 wk intervention, 2 wk. follow-up) Primary outcome: Change in HAM-D after 2wks active txt</p> <p><i>Interventions</i> G1: rTMS G2: sham stimulation</p> <p><i>Medications Allowed</i> ADs tapered for 9, 3 partial responders continued their medication</p> <p><i>Strategy</i> Mixed-within group differences</p> <p><i>Parameters</i> rTMS • Frequency (Hz):20 • Motor threshold (%): 80 • Number of trains: 20 • Length of train (seconds): 2</p>	<p><i>TRD definition</i> • Implied TRD, all patients had completed 1 or more medication trials but were depressed at study entry • Not required or not specified to be in current episode</p> <p><i>Tier 3</i></p> <p><i>Inclusion criteria</i> • DSM-IV criteria for current MDD • right-handed</p> <p><i>Exclusion criteria</i> • Pts w abnormalities on general & neurological exam, urine drug screen, HIV test, MRI scan of head), • Pacemakers • H/O seizures • H/O major head trauma</p>	<p><i>Treatment Failure</i></p> <p>Number of previous AD medications Overall: 13.4</p> <p><i>Polarity, %</i> Unipolar Overall: 91.7</p> <p>Bipolar II Overall: 8.3</p> <p><i>Age, mean yrs</i> Overall: 41.8 (12.4)</p> <p><i>Sex, % females</i> Overall: 91.7</p> <p><i>Right handed, %</i> Overall: 100</p> <p><i>HAM-D 21</i> Baseline n G1: 12 G2: 12</p> <p>Baseline score, mean (SD) Overall: 28.5 (4.2)</p>	<p><i>HAM-D 21</i> G1: rTMS G2: sham stimulation</p> <p>Change, mean (SD) At 2 weeks G1: -5.25 G2: +3.33 <i>P</i> < 0.03</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i></p> <p>Headache, % G1: 4/12 G2: NR</p> <p>Suicidality, % G1: 0 G2: Sham: 1/12</p> <p>Seizures: None</p> <p>Unexpected side effects: None</p> <p>Headaches NR by active v. sham</p> <p>Memory or Attention: None</p> <p><i>Attrition</i> Overall: 0</p> <p><i>Adherence/ compliance</i> N</p>

Evidence Table 39. KQ 4. Adherence: Tier 3 (rTMS vs. sham—MDD/Bipolar) (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Inter-train interval: NR • Pulses per session: • Total number of sessions: 5/wk for a total of 20 per patient <p>Sham:</p> <ul style="list-style-type: none"> • Same as above but angled at 45 degrees from skull 				

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Jorge et al., 2008⁶⁵ Experiment 1</p> <p><i>Country, setting</i> USA, university hospital, outpatients and inpatients</p> <p><i>Funding</i> NIMH</p> <p><i>Research Objective</i> To assess efficacy and safety of rTMS to treat vascular depression</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> m-ITT</p> <p><i>N</i> 30</p> <p><i>Duration</i> 3 weeks</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> None, all antidepressants discontinued</p> <p><i>Parameters</i> rTMS • Location of stimuli Left DLPC • Frequency 10 Hz • Intensity motor threshold. 110% • Pulses per session - 20 trains per day, seperated by 1 minute pauses total 12000 pulses • Number of sessions 10 in 10 days</p>	<p><i>TRD definition</i> • 1+ failed trials at an adequate dose • Required to be in current episode</p> <p>Tier 2</p> <p><i>Inclusion criteria</i> • Onset of major depressive disorder (as diagnosed by DSM-IV criteria) at age 50 years or older • history of subcortical stroke and/or at least 3 offollowing cardiovascular risk factors: arterial hypertension, diabetes mellitus, obesity, hyperlipidemia, and smoking</p> <p><i>Exclusion criteria</i> • Severe heart or respiratory failure, renal or hepatic failure, or occurrence of an ongoing neoplastic process, neurodegenerative disorders such as idiopathic Parkinson disease or probable Alzheimer disease</p>	<p><i>Subgroups</i> Age 50+</p> <p><i>Baseline N</i> G1: 15 G2: 15</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, %</i> All pts met criteria for MDD in current episode 20% only met criteria for minor depression at study entry</p> <p><i>Age, mean yrs</i> G1: 62.9 G2: 66.1</p> <p><i>Sex, % females</i> G1: 40 G2: 53</p> <p><i>HAM-D Baseline score, mean (SD)</i> G1: 19.5 (5.8) G2: 19.9 (5.4)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) G1: 33.1% G2: 13.6% <i>P</i> = 0.04</p> <p>Responders, n G1: 5 (33.3%) G2: 1 (6.7%) <i>P</i> = 0.08</p> <p>Remitters, n HAM-D17 < 8 and did not meet criteria for major or minor depression G1: 2 (13.3%) G2: 1 (6.7%) <i>P</i> = 0.5</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % NR</p> <p>Amnesia, % NR</p> <p>Cardiovascular adverse events, % NR</p> <p>Cognitive impairment, % NR</p> <p>Dizziness, % NR</p> <p>Headache, % G1: 33 G2: 27</p> <p>Insomnia, % NR</p> <p>Post op complications, % NR</p> <p>Somnolence, % NR</p> <p>Suicidality, % NR</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting, Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>Sham stimulation performed using a specially designed coil that looks exactly like standard stimulating coil but generates a small localized field that drops off very fast, producing a scalp sensation without actual cortical stimulation</p> <p><i>Strategy</i> Switch</p>	<ul style="list-style-type: none"> • patients with clinical evidence of dementia, actively suicidal, prominent psychotic features, or with comorbid alcohol or other drug abuse, • prior occurrence of induced seizures, major head trauma, and a history of epilepsy, metal in skull, cranial cavity, or brain parenchyma, • cardiac pacemaker, an implanted defibrillator, or a medication pump. 			<p>Additional Comments TCD-12K vs. Sham Local pain 7 vs. 7 Local discomfort 27 vs. 33 Anxiety 13 vs. 0 "There were no significant differences between active and sham stimulation groups infrequency of headaches or local discomfort. As expected, none of patients experienced a seizure. In addition, headaches were mild and responded in all cases to low doses of common analgesics." • Local pain 1 (7) vs. 1 (7) • Headaches 5 (33) vs. 4 (27) • Local discomfort 4 (27) vs. 5 (33) • Anxiety 2 (13) vs. 0</p> <p><i>Neuropsychological or executive functioning</i> Yes</p> <p>Measures, Results Variable Stimulation Group, Mean (SD) Scores</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>P</i> Value TCD-12K vs. Sham / TCD-18K vs. Sham Baseline values MMSE score 28.1 (1.6) vs. 26.9 (2.8) / 28.2 (1.4) vs. 28.6 (1.7) <i>P</i> = 0.61 RAVLT trials 1-5, score 42.1 (11.3) vs. 36.2 (12.4) / 41.7 (10.1) vs. 44.2 (9.6) <i>P</i> = 0.34 RAVLT delayed recall, score 7.6 (4.1) vs. 5.4 (2.4) / 7.5 (3.8) vs. 8.2 (3.3) <i>P</i> = 0.16 Trail Making Test B, s 124.8 (67.6) vs. 117.0 (58.7) / 99.5 (59.4) vs. 106.8 (63.0) <i>P</i> = 0.24 Stroop Color and Word Test, interference 29.7 (8.3) vs. 29.4 (11.7) / 33.5 (9.2) vs. 30.3 (10.0) <i>P</i> = 0.46 COWAT score 38.5 (14.0) vs. 27.7 (9.9) / 35.3 (11.4) vs. 39.6 (12.9) <i>P</i> = 0.08</p> <p>Compared with sham stimulation, active rTMS at TCD-12K and TCD- 18K was not associated with significant changes in ADLs as measured byFunctional Independence Measure</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>or in most neuropsychological tests assessing memory and executive functions. However, after controlling for baseline Trail Making Test B time, patients receiving active rTMS had significantly decreased (ie, improved) Trail Making Test B times compared with patients receiving sham stimulation, for TCD-12K group ($F=7.7$; $P=0.01$) and TCD-18K group ($F=4.9$; $P=0.03$). No significant differences in Trail Making Test B times between responders and nonresponders, suggesting this effect was independent of mood.</p> <p>Predefined No</p> <p><i>MMSE</i></p> <p>Baseline n G1: 15 G2: 15</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Baseline score, mean (SD) G1: 28.1 (1.6) G2: 26.9 (2.8)</p> <p>Endpoint score, mean (SD) NR</p> <p>Change, mean (SD) NR</p> <p><i>Other</i> "There were no significant differences between active and sham stimulation groups infrequency of headaches or local discomfort. As expected, none of patients experienced a seizure. In addition, headaches were mild and responded in all cases to low doses of common analgesics." Local pain 1 (7) vs. 1 (7) Headaches 5 (33) vs. 4 (27) Local discomfort 4 (27) vs. 5 (33) Anxiety 2 (13) vs. 0</p> <p>Adequate information No</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Attrition</i></p> <p>Overall, %</p> <ul style="list-style-type: none"> • 5 dropped out before first stimulation = 5% • Did not report if it was from experiment 1 or 2 • No reported attrition after first stimulation. <p>At end of treatment, % 0</p> <p>At end of followup, % 0</p> <p>Withdrawals due to efficacy, % 0</p> <p>Withdrawals due to adverse events, % 0</p> <p>Other 5 patients withdrew before stimulation began</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Jorge et al., 2004⁶⁶</p> <p><i>Country, setting</i> USA, single center, outpatients</p> <p><i>Funding</i> Charles A Dana Foundation Grant</p> <p><i>Research Objective</i> To test hypothesis - high frequency rTMS of left dorsolateral prefrontal cortex would produce a significant reduction of depressive symptoms without affecting cognitive status of patients</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 20</p> <p><i>Duration</i> Active: 2 weeks treatment with primary outcomes assessed at 1 week post rTMS txt.</p> <p><i>Interventions</i> G1: rTMS G2: Sham</p> <p><i>Medications Allowed</i> All AD tapered. No other drugs reported</p> <p><i>Strategy</i> Switch</p> <p><i>Parameters</i> rTMS</p> <ul style="list-style-type: none"> • Location of stimuli LDLPFC • Frequency 10 Hz • Intensity motor threshold. 110% • Pulses per session - 1600 (32 trains) • Number of sessions 10 over 2 weeks 	<p><i>TRD definition</i></p> <ul style="list-style-type: none"> • 2+ failed adequate trials (adequacy defined by ATHF) • Not required or not specified to be in current episode <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i></p> <ul style="list-style-type: none"> • Patients that had had a stroke and suffered from depression <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Presence of severe systemic disease or an ongoing neoplasia • Neurodegenerative disorders such as Parkinson disease or Alzheimer disease • Clinical evidence of dementia (MMSE scores less than 23) • aphasic patients with severe language comprehension deficits • actively suicidal or who presented with prominent psychotic features or a bipolar course • Evidence of alcohol or drug abuse during past 12 months 	<p><i>Subgroups</i> Stroke induced depression</p> <p><i>Treatment Failure</i> Mean failed trials, n (SD) G1: 3.8 G2: 3.8</p> <p><i>Polarity, %</i> 100% diagnosis of depression due to stroke 85% MDD 15% Minor Depression</p> <p><i>Age, mean yrs</i> G1: 63.1 G2: 66.5</p> <p><i>Sex, % females</i> G1: 40 G2: 50</p> <p><i>HAM-D 17</i> Baseline n G1: 10 G2: 10</p> <p>Baseline score, mean (SD) G1: 20.1 (6.7) G2: 20.8 (6.0)</p>	<p><i>HAM-D 17</i> Endpoint score, mean (SD) G1: 12.8 G2: NR</p> <p>Change, mean % At week 3 G1: -38% (-7.3 pts) G2: -13% <i>P</i> < 0.006</p> <p>Responders, n G1: 3 (30%) G2: 0 (0%) <i>P</i> = NS</p> <p>Remitters, n G1: 1 (10%) G2: 0 (0%) <i>P</i> = NS</p>	<p><i>Quality of Life</i> NR</p> <p><i>Adverse Events</i> Overall, % G1: NR</p> <p>Amnesia, % G1: NR</p> <p>Cardiovascular adverse events, % G1: NR</p> <p>Cognitive impairment, % G1: NR</p> <p>Dizziness, % G1: NR</p> <p>Headache, % G1: 30%</p> <p>Insomnia, % G1: 5%</p> <p>Post op complications, % G1: NR</p> <p>Somnolence, % G1: NR</p> <p>Suicidality, % G1: NR</p> <ul style="list-style-type: none"> • Transient headaches (six patients) relieved with low doses of

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<ul style="list-style-type: none"> • Prior occurrence of induced seizures, major head trauma • History of idiopathic epilepsy; metal in skull, cranial cavity, or brain parenchyma • Cardiac pacemaker, an implanted defibrillator, or intracardiac lines 			<p>acetaminophen, local discomfort at site of stimulation usually produced by tightness of stimulation cap (five patients), and an exacerbation of initial insomnia observed in one patient</p> <ul style="list-style-type: none"> • No significant differences infrequency of adverse events between active and sham rTMS groups • No patients with seizures or propagation of cortical excitability to ipsilateral motor cortex <p><i>Neuropsychological or executive functioning</i> Yes</p> <p>Measures, Results</p> <ul style="list-style-type: none"> • Neuropsychological variable at end point - mean (SD) • MMSE Scores 27.4 (3.0) vs. 26.5 (1.7) • RAVLT Scores, (delayed recall) 6.0 (3.2) vs. 5.2 (2.1) • COWAT Scores 36.0 (13.7) vs. 25.5 (6.5)

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<ul style="list-style-type: none"> • Trail Making Test B 144.4 (72.7) vs. 146.8 (62.4) • BNT Scores 26.8 (3.4) vs. 24.8 (3.9) <p>Predefined Yes</p> <p>MMSE</p> <p>Baseline n G1: 10 G2: 10</p> <p>Baseline score, mean (SD) G1: 25.9 G2: 26.4</p> <p>Endpoint score, mean (SD) G1: 27.4 (3.0) G2: 26.5 (1.7)</p> <p>Change, mean (SD) G1: +1.5 (1.3) G2: +0.1 (2.4)</p> <p>Other Mann–Whitney x-squared 1.8, df = 1, <i>P</i> = 0.18</p> <p>Adequate information No</p>

Evidence Table 40. KQ 5: Efficacy and harms for patient subpopulations (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<i>Attrition</i> Overall, % 0 At end of treatment, % 0 At end of follow up, % 0 Withdrawals due to efficacy, % 0 Withdrawals due to adverse events, % 0 Other NR <i>Adherence/ compliance</i> NR

Evidence Table 41. KQ 6: Quality of life

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Harley, 2008³⁶</p> <p><i>Country, setting</i> United States, university clinics, outpatient psychiatric</p> <p><i>Funding</i> Kaplan Fellowship Award Grant through Harvard Medical School</p> <p><i>Research Objective</i> To assess feasibility and potential utility of a Dialectical Behavior Therapy(DBT)-based skills training group for TRD</p> <p><i>Quality Rating</i> Fair</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> Completers</p> <p><i>N</i> 24</p> <p><i>Duration</i> Primary outcome after 16 weeks of active txt Follow up: 6 months</p> <p><i>Interventions</i> G1: DBT-based skills training G2: Wait-list Control</p> <p><i>Medications Allowed</i> Patients continued antidepressant therapy</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> • Type of therapy: Dialectical Behavior Therapy(DBT)-based skills training • Method: Group • Number of sessions/week:1 • Total number of sessions:16 G2: Wait list</p>	<p><i>TRD definition</i> • 1+ failed medications (6+ weeks at “standard effective dose”) • Not required or not specified to be in current episode</p> <p><i>Tier 2</i></p> <p><i>Inclusion criteria</i> • 18-65 years with a principal diagnosis of MDD • Established treatment relationship with a psychiatrist at MGH or in larger community. • Stabalized on an adequate dose of antidepressant medication before entering study.</p> <p><i>Exclusion criteria</i> • Borderline personality disorder, bipolar disorder, psychotic spectrum disorders, active substance abuse or dependence, mental retardation, or pervasive developmental disorder.</p>	<p><i>Baseline N</i> G1: 13 G2: 11</p> <p><i>Treatment Failure</i> Mean failed trials NR</p> <p><i>Polarity, % MDD</i></p> <p><i>Overall:</i> 100</p> <p><i>Age, mean yrs</i> Overall: 41.8</p> <p><i>Sex, % females</i> Overall: 75</p> <p><i>Race, % white</i> Overall: 83</p> <p><i>HAM-D 17</i> Baseline score, mean (SD) G1: 16.15 (4.47) G2: 18.64 (4.72) P = NS</p> <p><i>BDI</i> Baseline score, mean (SD) G1: 27.31 (8.83) G2: 27.44 (11.66) P = NS</p>	<p><i>HAM-D 17</i> Analyzed n G1: 10 G2: 9</p> <p>Endpoint score, mean (SD) Completers analysis, 16 weeks G1: 11.30 (5.3) G2: 17.11 (6.23)</p> <p>Change, mean (SD) Completers, 16 weeks G1: -5.6 G2: -1.78</p> <p><i>P < 0.05 Remitters, n</i> Completers per protocol analysis, 16 weeks G1: 3 (23%*) G2: 0 (0%*) P = NR</p> <p><i>BDI</i> Endpoint score, mean (SD) At Week 16, completers per protocol G1: 15.10 (12.13) G2: 25.89 (16.30)</p> <p>Change, mean (SD) G1: -12.80 G2: -1.55 P < 0.01</p>	<p><i>Quality of Life</i> <i>Lifework-The Range of Impaired Functioning Tool (LIFE-RIFT)</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 4.00 (0.94) G2: 3.44 (1.24)</p> <p>Endpoint score, mean (SD) G1: 2.70 (1.34) G2: 3.11 (1.69)</p> <p>Change, mean (SD) G1: -1.3 G2: -0.33 P = NS</p> <p><i>Social Adjustment Scale-Self-Report (SAS-SR) work subscale</i></p> <p>Baseline n G1: 10 G2: 9</p> <p>Baseline score, mean (SD) G1: 82.50 (21.21) G2: 69.22 (17.95)</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
		<ul style="list-style-type: none"> • Active suicidality requiring more intensive levels of care • Severe or unstable medical conditions • Previous or current CBT experience. 			<p>Endpoint score, mean (SD) G1: 65.70 (19.27) G2: 69.56 (17.66)</p> <p>Change, mean (SD) G1: -16.80 G2: 0.34 <i>P</i> < 0.05</p> <p><i>Adverse Events</i> NR</p> <p>MMSE NR</p> <p><i>Attrition</i> Overall, %: 21</p> <p>At end of treatment, % G1:23 G2:18</p> <p>At end of followup, % G1:20 G2: NR</p> <p>Withdrawals due to efficacy, % G1: 8 G2: 0</p> <p>Withdrawals due to adverse events, % 0</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>Other 5 participants (3 groups, 2 wait-lists) did not complete study. One group participant dropped out because of difficulty finding childcare another discontinued treatment due to a work schedule conflict, and third decided group was not a good fit. One wait-list participant moved and could not continue instudy and a medical problem preventedsecond from continuing.</p> <p><i>Adherence/ compliance</i> Compliance Participants completed a weekly check-in form asking about medication compliance overpreceding month.19 participants who completed study reported that they had been largely medication compliant—11 reported that they had taken their medication as directed every day and 8 reported that they had</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					forgotten a medication dose between 1 to 4 times in previous month.
<p><i>Author, Year</i> Fitzgerald et al., 2003¹⁵</p> <p><i>Country, setting</i> Australia 2 general psychiatric services, outpatients</p> <p><i>Funding</i> National Health and Medical Research Council and a grant from Stanley Medical Research Institute</p> <p><i>Research Objective</i> To evaluate efficacy of HFL-TMS and LFR-TMS in treatment-resistant depression and compared with a sham-treated control group</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> ITT</p> <p><i>N</i> 60</p> <p><i>Tier 1</i></p> <p><i>Duration</i> Primary endpoint after 2 weeks of txt, after which pts with <20% reduction in MADRS could cross over to the other active txt. Follow up assessment conducted at 2 weeks post txt.</p> <p><i>Interventions</i> G1: High Frequency rTMS G2: Low Frequency rTMS G3: Sham</p> <p><i>Medications Allowed</i> 46 patients continued (failed) AD medication while others were not on a med at study entry. Patients allowed mood</p>	<p><i>TRD definition</i> • Failed a minimum of 2 courses of antidepressant medications (6+ weeks)</p> <p>Not required or not specified to be in current episode</p> <p><i>Inclusion criteria</i> • DSM-IV diagnosis of Major Depression (included bipolar depression)</p> <p><i>Exclusion criteria</i> • Significant medical illnesses, neurologic disorders, or other Axis I psychiatric disorders</p>	<p><i>Treatment Failure</i> Mean failed trials Overall (SD) 5.68 (3.40) Polarity, %</p> <p>Bipolar I G1: 5 G2: 5 G3: 20</p> <p><i>Age, mean yrs</i> G1: 42.2 G2: 45.55 G3: 49.15</p> <p><i>Sex, % females</i> G1: 40 G2: 35 G3: 55</p> <p><i>Right handed, %</i> G1: 90 G2: 100 G3: 85</p> <p><i>BDI</i> Baseline n G1: 20 G2: 20 G3: 20</p>	<p><i>BDI</i> Endpoint score, mean (SD)</p> <p>At 2 weeks G1: 26.7 (11.9) G2: 27.2 (10.8) G3: 29.0 (8.7)</p> <p>Change, mean (SD) At 2 weeks G1: -6.4 G2: -7.8 G3: -2.3 P = 0.03</p> <p><i>MADRS</i> Endpoint score, mean (SD) At 2 weeks G1: 30.8 (7.8) G2: 32.2 (9.0) G3: 35.4 (7.5)</p> <p>Change, mean; % change, (SD) At 2 weeks G1: -5.25; 13.5% (16.7%) G2: -5.5; 15.0% (14.1%) G3: -0.35; 0.76% (16.2%) P = 0.004 G1: vs. G3, G2 vs. G3, P < 0.005</p>	<p><i>Quality of Life</i></p> <p>GAF Global Assessment of Functioning</p> <p>Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 43.00 (6.76) G2: 43.55 (9.94) G3: 42.75 (7.15)</p> <p>Endpoint score, mean (SD) At 2 weeks G1: 45.2 (7.1) G2: 46.3 (8.5) G3: 42.5 (6.8)</p> <p>Change, mean (SD) At 2 weeks G1: 2.2 G2: 2.85 G3: 0.5</p> <p>Overall group F56,2=2.6; P =.08; LFR-TMS vs sham: P = 0.03; and HFLTMS vs sham: P = 0.09</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>stabilizers and antipsychotics</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> rTMS LowFrequency (Hz):1 • Motor threshold (%): 100 • Number of trains: 60 • Length of train (seconds): 5 • Inter-train interval:60 • Pulses per session: 300 • Total number of sessions: 10 sessions daily, 5 days/week</p> <p>rTMS High • Frequency (Hz):10 • Motor threshold (%): 100 • Number of trains: 20 • Length of train (seconds): 5 • Inter-train interval: 25 • Pulses per session: 1000 • Total number of sessions: 10 sessions daily, 5 days/week</p>		<p>Baseline score, mean (SD) G1: 33.15 (12.12) G2: 35.05 (9.25) G3: 32.30 (9.10)</p> <p><i>MADRS</i> Baseline n G1: 20 G2: 20 G3: 20</p> <p>Baseline score, mean (SD) G1: 36.05 (7.55) G2: 37.70 (8.36) G3: 35.75 (8.14)</p>	<p>Responders, n 20% ≤ decrease At 2 weeks G1: 8 (40) G2: 7 (35) G3: 2 (10) P = 0.07</p> <p>Responders, n 50% ≤ decrease At 2 weeks G1: 0 G2: 1 (5) G3: 0 P = NR</p> <p><i>CGI</i> Endpoint score, mean (SD) NR P =.01</p>	<p><i>Quality of Life</i> Overall group F56,2=2.6; P =.08; LFR-TMS vs sham: P = 0.03; and HFLTMS vs sham: P = 0.09</p> <p><i>Adverse Events</i> Dizziness, % G1: 5% G2: 5% G3: 0 G4: 3.3%</p> <p>Other: 0- 2wks: • 7 (11%) of 60 patients reported site discomfort or pain during rTMS and 6 (10%) reported a headache after rTMS. • Although there was no difference in incidence of these adverse effects (P =.08), patients inHFL-TMS group seemed to report more discomfort during procedure itself. • Only 1 patient (HFL-TMS group) reported persistence ofheadache for longer than 1 hour.</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<p>Sham rTMS</p> <ul style="list-style-type: none"> • Coil angled 45 degrees offhead for 10 sessions daily, 5 days/week 				<ul style="list-style-type: none"> • Two patients (1 in each group) reported transient dizziness for a short time after treatment. <p>2wks - 4 wks:</p> <ul style="list-style-type: none"> • One patient withdrew after 1 session of HFL-TMS treatment in single-blind phase of study owing to site pain. • One bipolar patient, who had a successful response to LFR-TMS treatment, experienced a manic episode 10 days after completion of trial after ceasing treatment with valproate sodium <p><i>Neuropsychological or executive functioning</i></p> <ul style="list-style-type: none"> • No deterioration in performance was found in any cognitive measures in group as a whole or in analyses of patients who received HFL-TMS only LFR-TMS only, or both active treatment conditions • Including all patients who underwent at least 1 type of active treatment, there was a significant

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>improvement in performance on verbal paired associates ($t_{50} = -7.3$; $P < 0.001$), verbal fluency ($t_{48} = -3.8$; $P < 0.001$), and digit span forwards ($t_{48} = -1.8$; $P = 0.003$) subscales; Personal Semantic Memory Schedule ($t_{50} = -2.4$; $P = 0.02$); and Autobiographical Memory Schedule ($t_{50} = -1.9$; $P = 0.05$).</p> <ul style="list-style-type: none"> • A similar pattern of improvements was seen for each of treatment subgroups (HFL-TMS only, LFR-TMS only, or both active treatments). • Changes in performance on cognitive measures did not correlate with changes in MADRS and Beck Depression Inventory scores across same times. <p>MMSE NR</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p><i>Other</i></p> <p><i>Attrition</i> Overall, % None in initial 2 week treatment phase</p> <p>At end of treatment, % 0</p> <p>At end of followup, % NR But at least 28.3% did not continue on thru 2nd 2 weeks</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 0 (1 during followup) G2: 0 (0 during followup) G3: 0 (0 during followup) Progression of patients through 2nd phase is very unclear</p> <p><i>Adherence/ compliance</i> NR</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
<p><i>Author, Year</i> Rush et al., 2005²⁴ Carpenter et al., 2004²⁵</p> <p><i>Country, setting</i> US, multicente, outpatient psychiatric</p> <p><i>Funding</i> Cyberonics, Inc.</p> <p><i>Research Objective</i> To compare adjunctive VNS to sham in TRD patients</p> <p><i>Quality Rating</i> Good</p>	<p><i>Study design</i> RCT</p> <p><i>Type of analysis</i> m-ITT/PP for efficacy, ITT for Aes</p> <p><i>N</i> 235</p> <p><i>Duration</i> 10wks of stimulation Primary Outcome: HAM-D Response after 10wks txt</p> <p><i>Interventions</i> G1: VNS G2: Sham</p> <p><i>Medications allowed</i> pts allowed up to 5 antidepressants, mood stabilizers, or other psychotropic medications</p> <p><i>Strategy</i> Augmentation</p> <p><i>Parameters</i> VNS: Frequency (Hz): 20 Pulse width (seconds): 500 µs • On/Off cycle parameters: 30 sec on and 5 min off</p>	<p><i>TRD definition</i> • TRD (2-6 failures verified by the ATHF, with failures in tw different drug classes) • Required to be in current episode</p> <p><i>Tier 1</i></p> <p><i>Inclusion criteria</i> • Current Major Depressive Episode (MDE) of 2+ yrs OR 4+ MDE in lifetime, • age 18-80, HAM-D24>=20; • bipolar pts had to also be resistant, intolerant of, or have contraindications to lithium</p> <p><i>Exclusion criteria</i> • Atypical or psychotic features in any MDE • current rapid cycling bipolar disorder, delerium, dementia, amnesia • other cognitive disoder, suicidality • risks related to surgical implantation</p>	<p><i>Treatment Failure</i> Percent with 4-6 current episode failures G1: 46.5% G2: 40.0%</p> <p><i>Polarity, %</i> Unipolar G1: 88.4 G2: 90.9 Bipolar I G1: 5.4 G2: 3.6 Bipolar II G1: 6.3 G2: 5.5</p> <p><i>Age, mean yrs</i> G1: 47.0 G2: 45.9</p> <p><i>Sex, % females</i> G1: 59 G2: 66</p> <p><i>Race, % white</i> G1: 97 G2: 96</p> <p><i>HAM-D24</i> Baseline n G1: 119 G2: 116</p>	<p><i>HAM-D24</i> N analyzed G1: 112 G2: 110 Endpoint score, mean (SD) NR % change, mean (SD) G1: -16.3 (28.1) G2: -15.3 (25.5) P = 0.639 Responders, n G1: 17 (15.2%) G2: 11 (10.0%) P = 0.251 MADRS Endpoint score, mean (SD) NR % change, mean (SD) G1: -17.1 (31.2) G2: -12.4 (27.1) P = 0.208 Responders, n G1: 17 (15.2) G2: 12 (0.0) P = 0.378 <i>IDS</i> Endpoint score, mean (SD) NR</p>	<p><i>Quality of Life</i> Medical Outcomes Study Short Form-36 (MOS-SF36) Baseline n G1: 112/ N=107 QOL analysis G2: 110/ N=107 QOL analysis Baseline score, mean (SD) NR Endpoint score, mean (SD) NR Change, mean (SD) G1: physical component: -0.9 (8.3); mental component: 5.0 (11.6) G2: physical component -1.6(8.4); mental component: 4.0(10.2) Other Physical component between VNS and sham: P = 0.480, Mental Component between VNS and sham: P = 0.406</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
	<ul style="list-style-type: none"> • Duration of treatment: <p>Sham:</p> <ul style="list-style-type: none"> • Device implanted but not turned on 		<p>Baseline score, mean (SD) G1: 28.8(5.3) G2: 29.7(5.2)</p> <p>MADRS Baseline score, mean (SD) G1: 31.4(6.3) G2: 31.9(6.3)</p> <p>IDS Baseline n G1: 112 (115 randomized) G2: 110</p> <p>Baseline score, mean (SD) G1: 44.3(9.1) G2: 45.4(8.5)</p> <p>CGI-I Baseline n G1: 112 G2: 110</p>	<p>% change, mean (SD) G1: 21.2 (25.4) G2: 16.3 (26.2) <i>P</i> = 0.158</p> <p>Responders, n G1: 19 (17) G2: 8 (7.3) <i>P</i> = 0.032</p> <p>Remitters, n NR</p> <p>CGI-I Endpoint score, mean (SD) NR</p> <p>Achieving 1 or 2 score, %(SD) G1: 13.9 G2: 11.8 VNS v. Sham, <i>P</i> = 0.648</p>	<p><i>Adverse Events</i> Overall, % NR</p> <p>Cardiovascular adverse events, % G1: 5, palpitations 5 G2: 3</p> <p>Other:–</p> <ul style="list-style-type: none"> • voice alteration: 68% v 38% • cough increased: 29% v 9% • dyspnea: 23% v 14%, • dysphagia: 21% v 11%, • neck pain: 21% v 10%, • paresthesia: 16% v 10%, • vomiting: 11% vs. 12%, • laryngismus 11% v 2%, • dyspepsia 10 v 5 • wound infection 8% v 2%, • hypomania/mania (via Young Mania Scale): 1.7% (1pt with a prestudy dx of bipolar) v 0% <p>Overall SAEs 30, pts VNS: 13.4% (16/119). Sham: 12.1% (14/116) 12 events, involving 11</p>

Evidence Table 41. KQ 6: Quality of life (continued)

Study Citation, Country, Setting Funding, Research Objective	Study Design N Duration Comparison	Study Sample Inclusion, Exclusion Criteria	Baseline Characteristics	Remission/Response	Quality of Life Adverse Events Attrition
					<p>patients, were cases of worsening depression requiring hospitalization</p> <p>Cardiac SAEs during implantation: 1.7% v 0%</p> <p>COSTART used to code reported events</p> <p><i>Attrition</i></p> <p>Overall, % 1.3 (3/235)</p> <p>At end of treatment, % G1: 2.6 G2: 0</p> <p>At end of followup, % NR</p> <p>Withdrawals due to efficacy, % NR</p> <p>Withdrawals due to adverse events, % G1: 2.6 G2: 0</p> <p>9 pts had a protocol violation post randomization</p> <p><i>Adherence/ compliance</i> NR</p>

References

1. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety*. 2000;12(3):118-23.
2. Rosa MA, Gattaz WF, Pascual-Leone A, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):667-76.
3. Grunhaus L, Schreiber S, Dolberg OT, et al. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003:324-31.
4. Kocsis JH, Gelenberg AJ, Rothbaum BO, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: The REVAMP trial. *Archives of General Psychiatry*. US: American Medical Assn 2009:1178-88.
5. Chistyakov AV, Kaplan B, Rubichek O, et al. Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clin Neurophysiol*. 2005 Feb;116(2):386-92.
6. Hansen PE, Ravnkilde B, Videbech P, et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation Inferior to Electroconvulsive Therapy in Treating Depression. *J ECT*. 2010/03/31 ed 2010.
7. McLoughlin DM, Mogg A, Eranti S, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess*. 2007 Jul;11(24):1-54.
8. Eranti S, Mogg A, Pluck G, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry*. 2007 Jan;164(1):73-81.
9. Knapp M, Romeo R, Mogg A, et al. Cost-effectiveness of transcranial magnetic stimulation vs electroconvulsive therapy for severe depression: A multi-centre randomised controlled trial. *Journal of Affective Disorders* 2008:273-85.
10. Avery DH, Holtzheimer PE, 3rd, Fawaz W, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry*. 2006 Jan 15;59(2):187-94.
11. Avery DH, Holtzheimer PE, 3rd, Fawaz W, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis*. 2007 May;195(5):378-81.
12. Bocchio-Chiavetto L, Miniussi C, Zanardini R, et al. 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug resistant depression. *Neurosci Lett*. 2008 May 30;437(2):130-4.
13. Boutros NN, Gueorguieva R, Hoffman RE, et al. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Research*. 2002 Dec 2002;113(3):245-54.
14. Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*. 2006 Jan;163(1):88-94.
15. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003 Oct;60(10):1002-8.

16. Garcia-Toro M, Mayol A, Arnillas H, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders*. 2001 May 2001;64(2):271-5.
17. Garcia-Toro M, Salva J, Daumal J, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res*. 2006 Jan 30;146(1):53-7.
18. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry*. 2010/05/05 ed 2010:507-16.
19. Holtzheimer PE, 3rd, Russo J, Claypoole KH, et al. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety*. 2004;19(1):24-30.
20. Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression and Anxiety*. 2004;19(1):59-62.
21. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999:163-71.
22. Pallanti S, Bernardi S, Di Rollo A, et al. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience*. 2010/02/11 ed 2010:323-8.
23. Pascual-Leone A, Rubio B, Pallardo F, et al. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet*. 1996 Jul 27;348(9022):233-7.
24. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry*. 2005 Sep 2005;58(5):347-54.
25. Carpenter LL, Moreno FA, Kling MA, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biological Psychiatry*. 2004 Sep 2004;56(6):418-26.
26. Su T-P, Huang C-C, Wei IH. Add-On rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry*. 2005 Jul 2005;66(7):930-7.
27. Zheng H, Zhang L, Li L, et al. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. Netherlands: Elsevier Science 2010:1189-95.
28. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry*. 2000 Feb 2000;47(4):332-7.
29. Manes F, Jorge R, Morcuende M, et al. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics*. 2001 Jun 2001;13(2):225-31.
30. Moser DJ, Jorge RE, Manes F, et al. Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology* 2002:1288-90.
31. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007:1208-16.
32. Stern WM, Tormos JM, Press DZ, et al. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci*. 2007 Spring;19(2):179-86.

33. Wiles NJ, Hollinghurst S, Mason V, et al. A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: A pilot study. *Behavioural and Cognitive Psychotherapy*. 2008 Jan 2008;36(1):21-33.
34. Bortolomasi M, Minelli A, Fuggetta G, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res*. 2007 Mar 30;150(2):181-6.
35. George MS, Wassermann EM, Kimbrell TA, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry*. 1997 Dec;154(12):1752-6.
36. Harley R, Sprich S, Safren S, et al. Adaptation of dialectical behavior therapy skills training group for treatment-resistant depression. *J Nerv Ment Dis*. 2008 Feb;196(2):136-43.
37. Möller AL, Hjaltason Ó, Ívarsson Ó, et al. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P-sub-3-sub-0-sub-0 event-related potential. *Nordic Journal of Psychiatry*. 2006 2006;60(4):282-5.
38. Paykel ES, Scott J, Teasdale JD, et al. Prevention of relapse in residual depression by cognitive therapy. A controlled trial. *Archives of General Psychiatry*. 1999;56(9):829-35.
39. Kennedy N, Paykel ES. Treatment and response in refractory depression: results from a specialist affective disorders service. *J Affect Disord*. 2004 Jul;81(1):49-53.
40. West ED. Electric convulsion therapy in depression: a double-blind controlled trial. *Br Med J (Clin Res Ed)* 1981:355-7.
41. Bretlau LG, Lunde M, Lindberg L, et al. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry* 2008:41-7.
42. Folkerts HW, Michael N, Tölle R, et al. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. *Acta Psychiatr Scand*. 1997 Nov;96(5):334-42.
43. Moore RG, Blackburn I-M. Cognitive therapy in the treatment of non-responders to antidepressant medication: A controlled pilot study. *Behavioural and Cognitive Psychotherapy*. 1997 1997;25(3):251-9.
44. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* 2007:739-52.
45. Dannon PN, Dolberg OT, Schreiber S, et al. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals--preliminary report. *Biol Psychiatry*. 2002 Apr 15;51(8):687-90.
46. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder : A multicenter, randomized, double-blind, placebo-controlled study. Memphis, TN, ETATS-UNIS: Physicians Postgraduate Press 2007:11.
47. Berman RM, Fava M, Thase ME, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009/05/02 ed 2009:197-206.
48. Corya SA, Williamson D, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety* 2006:364-72.
49. Fang Y, Yuan C, Xu Y, et al. Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: A double-blind, randomized pilot study in a Chinese population. *Journal of Clinical Psychopharmacology*. US: Lippincott Williams & Wilkins 2010:357-64.

50. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry* 2006;1161-72.
51. Mazeh D, Shahal B, Aviv A, et al. A randomized, single-blind, comparison of venlafaxine with paroxetine in elderly patients suffering from resistant depression. *Int Clin Psychopharmacol* 2007;371-5.
52. Little JT, Kimbrell TA, Wassermann EM, et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol*. 2000 Apr;13(2):119-24.
53. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *Br J Psychiatry* 1999;12-6.
54. Shelton RC, Williamson DJ, Corya SA, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry* 2005;1289-97.
55. Thase ME, Corya SA, Osuntokun O, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*. US: Physicians Postgraduate Press 2007;224-36.
56. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of acute response to TMS in the treatment of major depression: relapse during a continuation pharmacotherapy extension study. *Society for Biological Psychiatry Annual Meeting*; 2007 May; San Diego, CA; 2007.
57. Solvason HB, Husain M, Fitzgerald PB, et al. TMS in the acute treatment of major depression: Improvements in functional status and quality of life. *Society of Biological Psychiatry Annual Meeting*. San Diego, CA 2007.
58. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation*. Netherlands: Elsevier Science 2010;187-99.
59. Scott J, Teasdale JD, Paykel ES, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual. *British Journal of Psychiatry*. 2000;177(NOV.):440-6.
60. Scott J, Palmer S, Paykel E, et al. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. *Br J Psychiatry*. 2003 Mar;182:221-7.
61. Paykel ES, Scott J, Cornwall PL, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. *Psychol Med*. 2005/04/22 ed 2005:59-68.
62. Grunhaus L, Dannon PN, Schreiber S, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry*. 2000 Feb 15;47(4):314-24.
63. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, et al. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry*. 2005 May;186:410-6.
64. O'Connor M, Brenninkmeyer C, Morgan A, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. *Cogn Behav Neurol*. 2003 Jun;16(2):118-27.
65. Jorge RE, Moser DJ, Acion L, et al. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2008 Mar;65(3):268-76.
66. Jorge RE, Robinson RG, Tateno A, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry*. 2004 Feb 15;55(4):398-405.

Appendix E. Abbreviations and Full Names of Diagnostic Scales and Other Instruments

Abbreviated Name	Complete Name of Measure or Instrument	Range or mean of Scores	Improvement Denoted by
AMI	Autobiographical Memory Interview ¹	0–63	Increase
AMS	Autobiographical Memory Schedule ¹	0–9	Increase
BSRT	Buschke Selective Reminding Test - 12 free recall trials of a 12 item word list; on each trial the patient is reminded only of items forgotten on the previous trial. ²	Varies	increase
CVLT	California Verbal Learning Test ³	Varies- results are based on overall and differences	Increase on overall- decrease on change
CAMCOG	The cognitive and self-contained part of the Cambridge Examination for Mental Disorders of the Elderly ⁴	0–107	Increase
	Digit span forwards ⁵	0–16	Increase
MMSE	Mini-mental state examination ⁶	0–30	Increase
PSMS	Personal Semantic Memory Schedule ¹	0–86	Increase
RAVLT	Rey Auditory Verbal Learning Test - The RAVLT consists of 15 nouns read aloud for five consecutive trials with each trial followed by a free-recall trial. The total score is the total number of words recalled through the five trials. ⁷	Varies	Increase
Stroop	The Stroop Color-Word Test ⁸	Varies	Increase
TMT Part A and B	Trail making test Part A and B ⁹	Mean - Part A 29 seconds Part B 75 seconds	Decrease
TNET	Transient News Events Test ¹⁰	Varies	Increase

References

1. Kopelman MD, Wilson BA, Baddeley AD. The autobiographical memory interview: a new assessment of autobiographical and personal semantic memory in amnesic patients. *J Clin Exp Neuropsychol* 1989;11(5):724–44.
2. Buschke H, Fuld PA. Evaluating storage, retention, and retrieval in disordered memory and learning. *Neurology* 1974;24(11):1019–25.
3. Delis DC, Freeland J, Kramer JH, Kaplan E. Integrating clinical assessment with cognitive neuroscience: Construct validation of the California Verbal Learning Test. *J Consult Clin Psychol* 1988;56(1):123–30.
4. De Koning I, Van Kooten F, Dippel DWJ, Van Harskamp F, Grobbee DE, Kluft C, et al. The CAMCOG: A Useful Screening Instrument for Dementia in Stroke Patients. *Stroke* 1998;29(10):2080–6.
5. Wechsler D. Technical manual for the Wechsler Adult Intelligence and Memory Scale-Third Edition. New York: The Psychological Corporation; 1997.
6. Folstein MF, Folstein SE, McHugh PR. “Mini-mental state.” A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 1975 Nov;12(3):189–98.
7. Lezak MD. *Neuropsychological assessment*. New York: Oxford University Press; 1995.
8. Golden CJ, Freshwater SM. *Stroop color and word test : a manual for clinical and experimental uses*. Chicago: Stoelting; 2002.
9. Corrigan JD, Hinkeldey NS. Relationships between parts A and B of the Trail Making Test. *Journal Of Clinical Psychology* 1987;43(4):402–9.
10. O'Connor MG, Sieggreen MA, Bachna K, et al. Long-term retention of transient news events. *Journal of the International Neuropsychological Society* 2000;6(1):44–51.

Appendix F. Characteristics of Studies With Poor Internal Validity

To assess the quality (internal validity or risk of bias) of studies, we used predefined criteria based on those described in the AHRQ Methods Guide for Comparative Effectiveness Reviews (ratings: good, fair, poor). Elements of quality assessment for trials included, among others, the methods used for randomization, allocation concealment, and blinding; the similarity of compared groups at baseline; maintenance of comparable groups; overall and differential loss to follow-up; and the use of intention-to-treat analysis. We assessed observational studies based on the potential for selection bias (methods of selection of subjects and loss to followup), potential for measurement bias (equality, validity, and reliability of ascertainment of outcomes), adjustment for potential confounders, and statistical analysis.

In general terms, a “good” study has the least bias and results are considered to be valid. A “fair” study is susceptible to some bias but probably not sufficient to invalidate its results. The fair-quality category is likely to be broad, so studies with this rating will vary in their strengths and weaknesses. A “poor” rating indicates significant bias (stemming from, e.g., serious errors in design, analysis reporting, large amounts of missing information, or discrepancies in reporting) that may invalidate the study’s results.

To systematically rate studies, we designed and used a structured data abstraction form. Trained reviewers abstracted data from each study and assigned an initial quality rating. A second reviewer read each abstracted article, evaluated the accuracy, completeness, and consistency of the data abstraction, and independently rated the quality. If differences in quality ratings could not be resolved by discussion, a third senior reviewer was involved. The full research team met regularly during the article abstraction period to discuss global issues related to the data abstraction process. The following lists all the studies reviewed and rated as poor quality, with their design and primary reasons for the final rating.

Study	Design	Primary Reasons for Poor Quality Rating
Key Question 1a		
Gregory, 1985 ¹	RCT	High potential for selection bias. Study does not report adequate information for assessment of bias, specifically regarding baseline characteristics. High rate of attrition. Study analysis was on completers only.
Grunhaus, 2000 ²	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy the other intervention group underwent and augmentative intervention strategy.
Wang, 2004 ³	RCT	High potential for selection bias. This article does not report adequate information for an assessment of bias, particularly regarding baseline differences and patient withdrawal from treatment. Inadequate reporting of randomization.
Key Question 1b		
Barker, 1987 ⁴	RCT	High potential for selection bias. Study does not report adequate information for an assessment of bias, particularly regarding baseline differences and patient withdrawal from treatment. Inadequate reporting of randomization techniques and reporting of statistical methodology. High attrition and modification of protocol.
Maes, 1996 ⁵	RCT	High potential for selection bias. No baseline information provided on TRD only group.

Study	Design	Primary Reasons for Poor Quality Rating
Sunderland, 1994 ⁶	RCT	High potential for measurement bias. Study does not report of any washout between crossovers. Study inadequately reports between group differences unable to asses differences on key outcomes (mean change, response, and remission).
Key Question 2		
Kauffmann, 2004 ⁷	RCT	High potential for measurement bias. Study does not provide numbers or methods for followup.
Key Question 3		
Grunhaus, 2000 ²	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy the other intervention group underwent and augmentative intervention strategy.
Key Question 4a		
Fitzgerald, 2006 ⁸	RCT	High potential for selection and measurement bias. Study poorly reports outcomes and to whom these outcomes are applicable.
Hansen, 2010 ⁹	RCT	High potential for selection bias. Analysis was performed on a subgroup of patients.
Frith, 1983; Frith, 1987 ^{10,11}	RCT	High potential for selection bias. Analyses concerning cognition were done on an undefined subgroup.
Key Question 4b		
Bortolomasi, 2007 ¹²	RCT	High potential for selection bias and measurement bias. Poor reporting. Study does not provide how adverse events were solicited (i.e., spontaneous admission or solicited by provider). Does not specify whether reports of adverse events were reported by active or sham patients.
Fitzgerald, 2003 ¹³	RCT	High potential for selection bias. No systematic method of data collection.
Fitzgerald, 2006 ⁸	RCT	High potential for selection bias. No systematic method of data collection.
Grunhaus, 2003 ¹⁴	RCT	High potential for selection bias. No systematic method of data collection.
Hansen, 2010 ⁹	RCT	High potential for selection bias. Analysis was performed on a subgroup of patients.
Holtzheimer, 2004 ¹⁵	RCT	High potential for selection and measurement bias. Does not provide how adverse events were solicited (i.e., spontaneous admission or solicited by provider).
Kauffmann, 2004 ⁷	RCT	High potential for measurement bias. Does not provide sufficient information to assess quality of data collection on adverse events.
Manes, 2001 ¹⁶	RCT	High potential for selection, measurement, and/or confounding bias. No methodology reported.
Padberg, 1999 ¹⁷	RCT	High potential for selection bias. No method of collection reported, it is unclear if pts in sham condition were included in assessment.
Rosa, 2006 ¹⁸	RCT	High potential for measurement bias. No systematic method of data collection.
Su, 2005 ¹⁹	RCT	High potential for selection bias. No systematic method of data collection.
Key Question 4d		
Grunhaus, 2000 ²	RCT	High potential for measurement bias. Patients did not receive the same amount of pulses. One intervention group underwent switch intervention strategy. The other intervention group underwent an augmentative intervention strategy.
Key Question 5		
Narushima, 2010 ²⁰	RCT	High potential for selection bias. Inadequate reporting of randomization techniques and reporting of statistical methodology. High rate of differential and overall attrition
Takahashi, 2009 ²¹		High potential for measurement and selection bias. Study does not compare between interventions. Inadequate reporting of randomization techniques.
Key Question 6		
Wiles, 2008 ²²	RCT	High potential for measurement bias. Scale used but outcomes not reported.

RCT = randomized controlled trial

References

1. Gregory S, Shawcross CR, Gill D. The Nottingham ECT study. A double-blind comparison of bilateral, unilateral and simulated ECT in depressive illness. *Br J Psychiatry* 1985;146(MAY):520-4.
2. Grunhaus L, Dannon PN, Schreiber S, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry* 2000 Feb 15;47(4):314-24. PMID: 10686266
3. Wang XM, Yang DB, Yu YF, et al. A controlled study of the treatment of repetitive transcranial magnetic stimulation in patients with major depression. *Chin J Clin Rehab* 2004;8(9):1770-1. PMID: 2004336095
4. Barker WA, Scott J, Eccleston D. The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol* 1987 Jul;2(3):261-72. PMID: 3121718
5. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *J Affect Disord* 1996;41(3):201-10 PMID: 8988452
6. Sunderland T, Cohen RM, Molchan S, et al. High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry* 1994;51(8):607-15. PMID: 7519005
7. Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression and Anxiety* 2004;19(1):59-62. PMID: 2004-11482-009
8. Fitzgerald PB, Benitez J, de Castella A, et al. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry* 2006 Jan;163(1):88-94. PMID: 16390894
9. Hansen PE, Ravnkilde B, Videbech P, et al. Low-frequency repetitive transcranial magnetic stimulation inferior to electroconvulsive therapy in treating depression. *J ECT* 2010 Mar 25. PMID: 20351570
10. Frith CD, Stevens M, Johnstone EC, et al. A comparison of some retrograde and anterograde effects of electroconvulsive shock in patients with severe depression. *Br J Psychol* 1987;78 (Pt 1):53-63. PMID: 3828659
11. Frith CD, Stevens M, Johnstone EC, et al. Effects of ECT and depression on various aspects of memory. *Br J Psychiatry* 1983;142:610-7. PMID: 6882984
12. Bortolomasi M, Minelli A, Fuggetta G, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res* 2007 Mar 30;150(2):181-6. PMID: 17303249
13. Fitzgerald PB, Brown TL, Marston NA, et al. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry* 2003 Oct;60(10):1002-8. PMID: 14557145
14. Grunhaus L, Schreiber S, Dolberg OT, et al. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003 Feb 15;53(4):324-31. PMID: 12586451
15. Holtzheimer PE, 3rd, Russo J, Claypoole KH, et al. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety* 2004;19(1):24-30. PMID: 14978782
16. Manes F, Jorge R, Morcuende M, et al. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr* 2001 Jun 2001;13(2):225-31. PMID: 2001-01938-006

17. Padberg F, Zwanzger P, Thoma H, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;88(3):163-71. PMID: 10622338
18. Rosa MA, Gattaz WF, Pascual-Leone A, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol* 2006 Dec;9(6):667-76. PMID: 16923322
19. Su T-P, Huang C-C, Wei IH. Add-On rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *J Clin Psychiatry* 2005 Jul 2005;66(7):930-7. PMID: 2005-08480-018
20. Narushima K, McCormick LM, Yamada T, et al. Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular depression. *J Neuropsychiatry Clin Neurosci* 2010;22(1):75-84. PMID: 20160213
21. Takahashi S, Mizukami K, Yasuno F, et al. Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy. *Psychogeriatrics* 2009;9(2):56-61. PMID: 19604326
22. Wiles NJ, Hollinghurst S, Mason V, et al. A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: A pilot study. *Behav Cognit Psychother* 2008 Jan 2008;36(1):21-33. PMID: 2008-15093-003

Appendix G. Articles by Database Searched

Cochrane Database = 82 articles (excluding duplicates)

1. Abbass Allan A, Hancock Jeffrey T, Henderson J, Kisely Steve R. Short-term psychodynamic psychotherapies for common mental disorders. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
2. Akechi T, Okuyama T, Onishi J, Morita T, Furukawa Toshi A. Psychotherapy for depression among incurable cancer patients. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2008.
3. Algul A, Sen H, Ates MA, Yen T, Durmaz O, Ozkan S, et al. [Propofol versus propofol-remifentanil combination anaesthesia in electroconvulsive therapy: effects on seizure duration and hemodynamics]. Klinik Psikofarmakoloji Bulteni 2009:24-8.
4. Bausewein C, Booth S, Gysels M, Higginson Irene J. Non-pharmacological interventions for breathlessness in advanced stages of malignant and non-malignant diseases. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2008.
5. Bisson J, Andrew M. Psychological treatment of post-traumatic stress disorder (PTSD). Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2007.
6. BlueCross BlueShield A. Transcranial magnetic stimulation for depression (Structured abstract). Chicago IL: Blue Cross Blue Shield Association (BCBS): Blue Cross Blue Shield Association (BCBS) 2009.
7. Brent D, Melhem N, Ferrell R, Emslie G, Wagner KD, Ryan N, et al. Association of FKBP5 polymorphisms with suicidal events in the Treatment of Resistant Depression in Adolescents (TORDIA) study. The American Journal of Psychiatry 2010:190-7.
8. Bschor T, Baethge C. No evidence for switching the antidepressant: systematic review and meta-analysis of RCTs of a common therapeutic strategy (Provisional abstract). Acta Psychiatrica Scandinavica 2010:174-9.
9. Burgess Sally SA, Geddes J, Hawton Keith KE, Taylor Matthew J, Townsend E, Jamison K, et al. Lithium for maintenance treatment of mood disorders. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2001.
10. Caldwell D, Hunot V, Moore Theresa HM, Davies P, Jones H, Lewis G, et al. Behavioural therapies versus treatment as usual for depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.
11. Callahan P, Hetrick Sarah E, Churchill R, Hunot V, Merry Sally N, Parker Alexandra G. Psychological therapies versus antidepressant medication, alone and in combination for depression in children and adolescents. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.
12. Christmas David MB, Crombie I, Eljamel S, Fineberg N, MacVicar B, Matthews K, et al. Neurosurgery for obsessive-compulsive disorder, other anxiety disorders and depressive disorders. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2005.
13. Churchill R, Caldwell D, Moore Theresa HM, Davies P, Jones H, Lewis G, et al. Behavioural therapies versus other psychological therapies for depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.

14. Churchill R, Davies P, Caldwell D, Moore Theresa HM, Jones H, Lewis G, et al. Humanistic therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
15. Churchill R, Davies P, Caldwell D, Moore Theresa HM, Jones H, Lewis G, et al. Interpersonal, cognitive analytic and other integrative therapies versus treatment as usual for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
16. Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, et al. Brief cognitive-behavioural therapies versus other brief psychological therapies for depression. *Cochrane Database of Systematic Reviews*. 2007(2).
17. Churchill R, Hunot V, Corney R, Knapp M, McGuire H, Tylee A, et al. Brief psychological therapies versus treatment as usual for depression. *Cochrane Database of Systematic Reviews*. 2007(2).
18. Churchill R, Moore Theresa HM, Caldwell D, Davies P, Jones H, Furukawa Toshi A, et al. Cognitive behavioural therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
19. Churchill R, Moore Theresa HM, Davies P, Caldwell D, Jones H, Lewis G, et al. Psychodynamic therapies versus other psychological therapies for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
20. Churchill R, Moore Theresa HM, Davies P, Caldwell D, Jones H, Lewis G, et al. Mindfulness-based 'third wave' cognitive and behavioural therapies versus treatment as usual for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
21. Claudino Angélica M, Hay Phillipa PJ, Silva de Lima M, Schmidt Ulrike US, Bacaltchuk J, Treasure J. Antipsychotic drugs for anorexia nervosa. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
22. Davies P, Hunot V, Moore Theresa HM, Caldwell D, Jones H, Lewis G, et al. Humanistic therapies versus treatment as usual for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
23. Duehmke Rudolf M, Hollingshead J, Cornblath David R. Tramadol for neuropathic pain. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006.
24. Gibbon S, Duggan C, Stoffers J, Huband N, Völlm Birgit A, Ferriter M, et al. Psychological interventions for antisocial personality disorder. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
25. Gregory RJ, DeLucia-Deranja E, Mogle JA. Dynamic deconstructive psychotherapy versus optimized community care for borderline personality disorder co-occurring with alcohol use disorders: a 30-month follow-up. *The Journal of nervous and mental disease* 2010:292-8.
26. Gupta A, Durham R. Cognitive behavioural therapy (CBT) for adults with HIV. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
27. Hay Phillipa PJ, Bacaltchuk J, Byrnes Roanna T, Claudino Angélica M, Ekmejian Avedis A, Yong Poh Y. Individual psychotherapy in the outpatient treatment of adults with anorexia nervosa. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2003.
28. He L, Guo J, Zhou M, Yang M, Zhu C. Repetitive transcranial magnetic stimulation for the treatment of amyotrophic lateral sclerosis or motor neuron disease. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
29. Herrmann LL, Ebmeier KP. Factors modifying the efficacy of transcranial magnetic stimulation in the treatment of depression: a review (Structured abstract). *Journal of Clinical Psychiatry*. 2006(12):1870-6.

30. Hilton Malcolm P, Stuart Emma L. Ginkgo biloba for tinnitus. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2004.
31. Hoffbrand Sara E, Howard L, Crawley H. Antidepressant treatment for post-natal depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2001.
32. Hunot V, Moore Theresa HM, Caldwell D, Davies P, Jones H, Furukawa Toshi A, et al. Cognitive behavioural therapies versus treatment as usual for depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.
33. Hunot V, Moore Theresa HM, Caldwell D, Davies P, Jones H, Lewis G, et al. Interpersonal, cognitive analytic and other integrative therapies versus other psychological therapies for depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.
34. Hunot V, Moore Theresa HM, Caldwell D, Davies P, Jones H, Lewis G, et al. Mindfulness-based 'third wave' cognitive and behavioural therapies versus other psychological therapies for depression. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2010.
35. Ipser Jonathan C, Carey P, Dhansay Y, Fakier N, Seedat S, Stein Dan J. Pharmacotherapy augmentation strategies in treatment-resistant anxiety disorders. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
36. Ipser Jonathan C, Pillay Nirvana S, Stein Dan J, van Honk J. Transcranial magnetic stimulation for post-traumatic stress disorder. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2007.
37. Ipser Jonathan C, Sander C, Stein Dan J. Pharmacotherapy and psychotherapy for body dysmorphic disorder. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2009.
38. Ipser Jonathan C, Stein Dan J. Newer anticonvulsants in the treatment of anxiety disorders. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
39. Ipser Jonathan C, Stein Dan J, Hawkrigde S, Hoppe L. Pharmacotherapy for anxiety disorders in children and adolescents. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2009.
40. Jackson Kenneth C, Lipman Arthur G. Drug therapy for anxiety in adult palliative care patients. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2004.
41. Jayaram Mahesh B, Hosalli P, Stroup TS. Risperidone versus olanzapine for schizophrenia. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2006.
42. Jones C, Cormac I, Silveira da Mota Neto Joaquim I, Campbell C. Cognitive behaviour therapy for schizophrenia. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2004.
43. Justo L, Soares Bernardo Garcia de O, Calil H. Family interventions for bipolar disorder. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2007.
44. Kang JI, Kim CH, Namkoong K, Lee CI, Kim SJ. A randomized controlled study of sequentially applied repetitive transcranial magnetic stimulation in obsessive-compulsive disorder. The Journal of clinical psychiatry 2009;1645-51.
45. Komossa K, Depping Anna M, Kissling W, Leucht S. Second-generation antipsychotic drugs for obsessive compulsive disorder. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2009.
46. Leucht S, Kissling W, McGrath J. Lithium for schizophrenia. Cochrane Database of Systematic Reviews. Chichester, UK: John Wiley & Sons, Ltd; 2007.

47. Leucht S, Kissling W, McGrath J, White P. Carbamazepine for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
48. Li Y, Zeng Rui F, Zheng D. Acupuncture for tinnitus. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2009.
49. Liu X, Zhang M, He L, Li Y. Chinese herbs combined with Western medicine for severe acute respiratory syndrome (SARS). *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006.
50. Maneeton N, Srisurapanont M. Tricyclic antidepressants for depressive disorders in children and adolescents: a meta-analysis of randomized-controlled trials (Structured abstract). *Journal of the Medical Association of Thailand* 2000:1367-74.
51. Marques Luciana de O, Soares B, Silva de Lima M. Trifluoperazine for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2004.
52. Moore Theresa HM, Hunot V, Davies P, Caldwell D, Jones H, Lewis G, et al. Psychodynamic therapies versus treatment as usual for depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
53. Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials (Structured abstract). *American Journal of Psychiatry* 2009:980-91.
54. O'Connell Neil E, Wand Benedict M, Marston L, Spencer S, DeSouza Lorraine H. Non-invasive brain stimulation techniques for chronic pain. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
55. Oude Voshaar Richard C, Hendriks GJ, Keijsers G, van Balkom Anton J. Cognitive behavioural therapy for anxiety disorders in later life. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2009.
56. Papakostas GI, Mischoulon D, Shyu I, Alpert JE, Fava M. S-adenosyl methionine (SAME) augmentation of serotonin reuptake inhibitors for antidepressant nonresponders with major depressive disorder: a double-blind, randomized clinical trial. *The American journal of psychiatry* 2010:942-8.
57. Ramaratnam S, Baker Gus A, Goldstein Laura H. Psychological treatments for epilepsy. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2008.
58. Rodriguez-Martin José L, Barbanoj José M, Schlaepfer TE, Clos Susana SC, Pérez V, Kulisevsky J, et al. Transcranial magnetic stimulation for treating depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2001.
59. Roxburgh C, Cook J, Dublin N. Anticholinergic drugs versus other medications for overactive bladder syndrome in adults. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
60. Saarto T, Wiffen Philip J. Antidepressants for neuropathic pain. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
61. Schwarz C, Hartung B, Leucht S. Benperidol for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.
62. Seitz Dallas P, Adunuri N, Gill S, Gruneir A, Herrmann N, Rochon P. Antidepressants for agitation and psychosis in dementia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
63. Shek E, Bardhan S, Cheine Maxim V, Ahonen J, Wahlbeck K. Beta-blocker supplementation of standard drug treatment for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2001.
64. Shek E, Stein Airton T, Shansis Flavio M, Marshall M, Crowther R, Tyrer P. Day hospital versus outpatient care for people with schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2009.

65. Stein Dan J, Ipser Jonathan C, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006.
66. Stein Dan J, Ipser Jonathan C, van Balkom Anton J. Pharmacotherapy for social anxiety disorder. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2000.
67. Tharyan P, Adams Clive E. Electroconvulsive therapy for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.
68. Timmer A, Jantschek G, Moser G, Motschall E, Preiss Jan C, Rücker G. Psychological interventions for treatment of inflammatory bowel disease. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2008.
69. Tsoi Daniel T, Porwal M, Webster Angela C. Interventions for smoking cessation and reduction in individuals with schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2010.
70. Tuunainen A, Kripke Daniel F, Endo T. Light therapy for non-seasonal depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2004.
71. Uthman Olalekan A, Abdulmalik Jubril O. Adjunctive therapies for AIDS dementia complex. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2008.
72. Van Der Wurff FB, Stek ML, Hoogendijk WJ, Beekman AT. The efficacy and safety of ECT in depressed older adults: a literature review (Brief record). *International Journal of Geriatric Psychiatry*. 2003(10):894-904.
73. Vasudev A, Macritchie K, Rao Sanjay NK, Geddes J, Young Allan H. Tiagabine in the maintenance treatment of bipolar disorders. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006.
74. Vasudev A, Macritchie K, Rao Sanjay NK, Geddes J, Young Allan H. Tiagabine in the treatment of acute affective episodes in bipolar disorder. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2006.
75. Veronese A, Hunot V, Cipriani A, Churchill R, Barbui C. Psychological therapies versus pharmacotherapy for obsessive compulsive disorder. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2008.
76. Volz A, Khorsand V, Gillies D, Leucht S. Benzodiazepines for schizophrenia. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2007.
77. Whale R, Terao T, Cowen P, Freemantle N, Geddes J. Pindolol augmentation of serotonin reuptake inhibitors for the treatment of depressive disorder: a systematic review (Provisional abstract). *Journal of Psychopharmacology* 2010:513-20.
78. Wiffen Philip J, Derry S, Moore RA, McQuay Henry J. Carbamazepine for acute and chronic pain in adults. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.
79. Wijkstra J, Lijmer J, Balk F, Geddes J, Nolen Willem A. Pharmacological treatment for psychotic depression. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.
80. Wilson K, Mottram PG, Vassilas C. Psychotherapeutic treatments for older depressed people. *Cochrane Database of Systematic Reviews*. 2008(1).
81. Zakrzewska Joanna M, Forssell H, Glenny A-M. Interventions for the treatment of burning mouth syndrome. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2005.

**EMBASE Database = 390 articles
(excluding duplicates)**

1. The new antidepressant agent venlafaxine is effective in therapy resistance. [German]. *Fortschritte der Medizin*. 1997;115(4).
2. Opinion and evidence in neurology and psychiatry. *CNS Drugs*. 2003;17(6):449-56.
3. Adli M, Bschor T, Bauer M, Lucka C, Lewitzka U, Ising M, et al. Long-term outcome after lithium augmentation in unipolar depression: Focus on HPA system activity. *Neuropsychobiology*. 2009 September;60 (1):23-30.
4. Aizenstein HJ, Reynolds III CF. The treatment of geriatric depression: progress and challenges. *Economics of Neuroscience* 2001;3(7):58-62.
5. Akcaboy ZN, Akcaboy EY, Yigitbasi B, Bayam G, Dikmen B, Gocus N, et al. Effects of remifentanyl and alfentanil on seizure duration, stimulus amplitudes and recovery parameters during ECT. *Acta Anaesthesiologica Scandinavica* 2005;49(8):1068-71.
6. Aklillu E, Karlsson S, Zachrisson OO, Ozdemir V, Agren H. Association of MAOA gene functional promoter polymorphism with CSF dopamine turnover and atypical depression. *Pharmacogenetics and Genomics*. 2009 April;19 (4):267-75.
7. Albert U, Brunatto C. Obsessive-compulsive disorder in adults: Efficacy of combined and sequential treatments. *Clinical Neuropsychiatry*. 2009;6 (2):83-93.
8. Allen LA, Woolfolk RL, Lehrer PM, Gara MA, Escobar JI. Cognitive behavior therapy for somatization disorder: A preliminary investigation. *Journal of Behavior Therapy and Experimental Psychiatry*. 2001;32(2):53-62.
9. Alonso P, Pujol J, Cardoner N, Benlloch L, Deus J, Menchon JM, et al. Right prefrontal repetitive transcranial magnetic stimulation in obsessive-compulsive disorder: A double-blind, placebo-controlled study. *Am J Psychiatry* 2001;158(7):1143-5.
10. Ananth J, Wohl M, Ranganath V, Beshay M. Rapid cycling patients: Conceptual and etiological factors. *Neuropsychobiology*. 1993;27(4):193-8.
11. Anderson DN. Treating depression in old age: the reasons to be positive. *Age and Ageing*. 2001;30(1):13-7.
12. Anderson SW, Booker MB. Cognitive behavioral therapy versus psychosurgery for refractory obsessive-compulsive disorder [1]. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2006;18(1):129.
13. Andersson G, Kaldö V. Internet-based cognitive behavioral therapy for tinnitus. *J Clin Psychol*. 2004 Feb;60(2):171-8.
14. Angelucci F, Ricci V, Martinotti G, Caltagirone C, Bria P. Paliperidone for treatment of obsessive compulsive resistant symptoms in schizophrenia: A case report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2009 01 Oct;33 (7):1277-8.
15. Anttila S, Viikki M, Huuhka K, Huuhka M, Huhtala H, Rontu R, et al. TPH2 polymorphisms may modify clinical picture in treatment-resistant depression. *Neuroscience Letters*. 2009 16 Oct;464 (1):43-6.
16. Arya A, Singh M, Gurwara AK. A comparison of thiopentone sodium, propofol and midazolam for electroconvulsive therapy. *Journal of Anaesthesiology Clinical Pharmacology*. 2008;24(3):291-4.
17. Asaknow JR, Emslie G, Clarke G, Wagner KD, Spirito A, Vitiello B, et al. Treatment of selective serotonin reuptake inhibitor-resistant depression in adolescents: predictors and moderators of treatment response. *J Am Acad Child Adolesc Psychiatry*. 2009;48(3):330-9.
18. Auriacombe M, Grabot D, Lincheneau PM, Zeiter D, Tignol J. Use of midazolam for ECT anesthesia: effects on antidepressive efficacy and seizure duration. Preliminary findings. *Eur Psychiatry* 1995;10(6):312-6.
19. Avramov MN, Stool LA, White PF, Husain MM. Effects of nicardipine and labetalol on the acute hemodynamic response to electroconvulsive therapy. *Journal of Clinical Anesthesia*. 1998;10(5):394-400.

20. Aydemir O, Deveci A, Taskin EO. Mirtazapine combination in treatment-resistant major depressive disorder: A retrospective evaluation of six weeks. *Klinik Psikofarmakoloji Bulteni*. 2009;19 (4):347-52.
21. Aziz M, Mehringer AM, Mozurkewich E, Razik GN. Cost-utility of 2 maintenance treatments for older adults with depression who responded to a course of electroconvulsive therapy: Results from a decision analytic model. *Can J Psychiatry*. 2005;50(7):389-97.
22. Aziz R, Lorberg B, Tampi RR. Treatments for late-life bipolar disorder. *Am J Geriatr Pharmacother*. 2006;4(4):347-64.
23. Bachar E, Lerer B, Shapira B. Increment in reminiscing after ECT: possible connections to neuropsychologic changes [2]. *J ECT*. 1999;15(2):165-6.
24. Baeken C, De Raedt R, Leyman L, Schiettecatte J, Kaufman L, Poppe K, et al. The impact of one HF-rTMS session on mood and salivary cortisol in treatment resistant unipolar melancholic depressed patients. *J Affect Disord*. 2009 Feb;113(1-2):100-8.
25. Baeken C, De Raedt R, Santermans L, Zeeuws D, Vanderhasselt MA, Meers M, et al. HF-rTMS treatment decreases psychomotor retardation in medication-resistant melancholic depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010 May;34(4):684-7.
26. Baeken C, De Raedt R, Vanderhasselt MA, Leyman L, Schiettecatte J, Poppe K, et al. A "hypersensitive" hypothalamic-pituitary-adrenal system could be indicative for a negative clinical high-frequency repetitive transcranial magnetic stimulation outcome in melancholic depressed patients. *Brain Stimulation* 2010:54-7.
27. Bailine S, Fink M, Knapp R, Petrides G, Husain MM, Rasmussen K, et al. Electroconvulsive therapy is equally effective in unipolar and bipolar depression. *Acta Psychiatrica Scandinavica*. 2010 June;121(6):431-6.
28. Bajbouj M, Merkl A, Schlaepfer TE, Frick C, Zobel A, Maier W, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *Journal of Clinical Psychopharmacology*. 2010 June;30(3):273-81.
29. Baldwin RC. Research into depressive disorder in later life: who is doing what? A literature search from 1998-2001. *Int Psychogeriatr*. 2002;14(4):335-46.
30. Barocka A, Flugel D. Treatment resistant depression. [German]. *Nervenheilkunde*. 1989;8(6):253-7.
31. Bauer J, Hageman I, Dam H, Baez A, Bolwig T, Roed J, et al. Comparison of propofol and thiopental as anesthetic agents for electroconvulsive therapy: A randomized, blinded comparison of seizure duration, stimulus charge, clinical effect, and cognitive side effects. *Journal of ECT*. 2009 June;25(2):85-90.
32. Bauer M. Absolutely therapy-resistant depression and mixed movement disorder in an unusual case of polycythemia vera. *Pharmacopsychiatry*. 1995;28(2):66-8.
33. Bauer M, Hellweg R, Baumgartner A. High dose thyroxine in patients with therapy- and prophylaxis-resistant affective disorders. [German]. *Nervenarzt*. 1998;69(11):1019-22.
34. Bauer MS. The collaborative practice model for bipolar disorder: design and implementation in a multi-site randomized controlled trial. *Bipolar Disorders*. 2001;3(5):233-44.
35. Bech P, Stokes PE, Greden JF, Tollefson GD. Acute therapy of depression. *Journal of Clinical Psychiatry*. 1993;54(8 SUPPL):18-27.
36. Benedetti F, Barbini B, Fulgosi MC, Colombo C, Dallaspesza S, Pontiggia A, et al. Combined total sleep deprivation and light therapy in the treatment of drug-resistant bipolar depression: Acute response and long-term remission rates. *Journal of Clinical Psychiatry*. 2005;66(12):1535-40.

37. Benitez-Rosario MA, McDarby G, Doyle R, Fabby C. Chronic Cluster-Like Headache Secondary to Prolactinoma: Uncommon Cephalgia in Association with Brain Tumors. *Journal of Pain and Symptom Management*. 2009 February;37 (2):271-6.
38. Bennett HA, Einarson A, Taddio A, Koren G, Einarson TR. Depression during pregnancy: Overview of clinical factors. *Clin Drug Investig*. 2004;24(3):157-79.
39. Birkenhager TK, Van Den Broek WW, Mulder PGH, De Lely A. One-year outcome of psychotic depression after successful electroconvulsive therapy. *J ECT*. 2005;21(4):221-6.
40. Bitonti AJ, Sjoerdsma A, McCann PP, Kyle DE, Oduola AMJ, Rossan RN, et al. Reversal of chloroquine resistance in malaria parasite *Plasmodium falciparum* by desipramine. *Science*. 1988;242(4883):1301-3.
41. Blatt SJ, Sanislow III CA, Zuroff DC, Pilkonis PA. Characteristics of effective therapists: further analyses of data from the National Institute of Mental Health Treatment of Depression Collaborative Research Program. *J Consult Clin Psychol*. 1996;64(6):1276-84.
42. Boggio PS, Rocha M, Oliveira MO, Fecteau S, Cohen RB, Campanha C, et al. Noninvasive brain stimulation with high-frequency and low-intensity repetitive transcranial magnetic stimulation treatment for posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2010 August;71 (8):992-9.
43. Bozhuyuk E, Poyraz CA, Poyraz BC, Ozdemir A, Savrun BM, Arikan MK. Persistent hiccups with fluvoxamine: A case report. *Yeni Symposium*. 2009;47(4):161-3.
44. Braslow JT, Duan N, Starks SL, Polo A, Bromley E, Wells KB. Generalizability of studies on mental health treatment and outcomes, 1981 to 1996. *Psychiatr Serv*. 2005;56(10):1261-8.
45. Brosse AL, Sheets ES, Lett HS, Blumenthal JA. Exercise and the treatment of clinical depression in adults: Recent findings and future directions. *Sports Med*. 2002;32(12):741-60.
46. Calabrese JR, Vieta E, El-Mallakh R, Findling RL, Youngstrom EA, Elhaj O, et al. Mood state at study entry as predictor of the polarity of relapse in bipolar disorder. *Biol Psychiatry*. 2004;56(12):957-63.
47. Calvert NW, Burch SP, Fu AZ, Reeves P, Thompson TR. The cost-effectiveness of lamotrigine in the maintenance treatment of adults with bipolar I disorder. *J Manag Care Pharm*. 2006;12(4):322-30.
48. Cassano GB, Jori MC. Efficacy and safety of amisulpride 50 mg versus paroxetine 20 mg in major depression: A randomized, double-blind, parallel group study. *International Clinical Psychopharmacology*. 2002;17(1):27-32.
49. Cassidy F, Weiner RD, Cooper TB, Carroll BJ. Combined catecholamine and indoleamine depletion following response to ECT. *British Journal of Psychiatry*. 2010 June;196(6):493-4.
50. Chandler GM, Iosifescu DV, Pollack MH, Targum SD, Fava M. Validation of the massachusetts general hospital Antidepressant Treatment History Questionnaire (ATRQ). *CNS Neuroscience and Therapeutics*. 2010 October;16 (5):322-5.
51. Chapouthier G, Venault P. Mouse strains selected for differences in sensitivity to a benzodiazepine receptor inverse agonist: Pharmacological and behavioural responses. *Biogenic Amines*. 2002;17(3):185-97.
52. Chaput Y, Magnan A, Gendron A. The co-administration of quetiapine or placebo to cognitive-behavior therapy in treatment refractory depression: a preliminary trial. *BMC Psychiatry*. 2008;8:73.
53. Chaturvedi R, Sharma A, Sorrell JH. Electroconvulsive therapy in patients with vagus nerve stimulation. *Journal of ECT*. 2009 June;25(2):141-3.
54. Cheam EWS, Critchley LAH, Chui PT, Yap JCM, Ha VWS. Low dose mivacurium is less effective than succinylcholine in electroconvulsive therapy. *Can J Anaesth*. 1999;46(1):49-51.

55. Cheema FA, Badr A, Iqbal J. Glioblastoma multiforme presenting as treatment-resistant depression. *Journal of Neuropsychiatry and Clinical Neurosciences*. 2010 Winter;22 (1):E26.
56. Chen PH, Cheng SJ. Restless legs syndrome among the elderly. *International Journal of Gerontology*. 2009 December;3 (4):197-203.
57. Choukalas CG, Walter J, Glick D, O'Connor MF, Tung A, Dinwiddie SH, et al. Mask ventilation, hypocapnia, and seizure duration in electroconvulsive therapy. *Journal of Clinical Anesthesia*. 2010;22 (6):415-9.
58. Citrome L. A review of aripiprazole in the treatment of patients with schizophrenia or bipolar I disorder. *Neuropsychiatr Dis Treat*. 2006;2(4):427-43.
59. Cohen RB, Boggio PS, Fregni F. Risk factors for relapse after remission with repetitive transcranial magnetic stimulation for the treatment of depression. *Depression and Anxiety*. 2009 July;26(7):682-8.
60. Cooper M. Cognitive behaviour therapy in an in-patient with chronic difficulties: A case report. *Behavioural and Cognitive Psychotherapy*. 1994;22(2):171-6.
61. Cotterill JA. Body dysmorphic disorder. *Dermatologic Clinics*. 1996;14(3):457-63.
62. Couturier JL. Efficacy of rapid-rate repetitive transcranial magnetic stimulation in the treatment of depression: A systematic review and meta-analysis. *J Psychiatry Neurosci*. 2005;30(2):83-90.
63. Dabkowska M, Rybakowski JK. Moclobemide in treatment-resistant depression. *European Neuropsychopharmacology*. 1993;3(3):328-9.
64. Daly JJ, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. ECT in bipolar and unipolar depression: Differences in speed of response. *Bipolar Disorders* 2001;3(2):95-104.
65. Dannon PN, Grunhaus L. Repetitive transcranial magnetic stimulation is effective following repeated courses in the treatment of major depressive disorder--a case report. *Hum Psychopharmacol*. 2003 Jun;18(4):313-5.
66. Daughters SB, Magidson JF, Schuster RM, Safren SA. ACT HEALTHY: A Combined Cognitive-Behavioral Depression and Medication Adherence Treatment for HIV-Infected Substance Users. *Cognitive and Behavioral Practice*. 2010 August;17 (3):309-21.
67. De Mendonca Lima CA. The pharmacokinetic of antidepressants and resistant depressions. [Portuguese]. *Jornal Brasileiro de Psiquiatria*. 1988;37(3):149-55.
68. Dell'Osso B, Altamura AC. Augmentative transcranial magnetic stimulation (TMS) combined with brain navigation in drug-resistant rapid cycling bipolar depression: A case report of acute and maintenance efficacy. *World Journal of Biological Psychiatry*. 2009;10(4 PART 2):673-6.
69. Denys D, Mantione M, Figuee M, Van Den Munckhof P, Koerselman F, Westenberg H, et al. Deep brain stimulation of the nucleus accumbens for treatment-refractory obsessive-compulsive disorder. *Archives of general psychiatry*. 2010 October;67 (10):1061-8.
70. Devinsky O, Duchowny MS. Seizures after convulsive therapy: a retrospective case survey. *Neurology*. 1983 Jul;33(7):921-5.
71. Diazgranados N, Ibrahim L, Brutsche NE, Newberg A, Kronstein P, Khalife S, et al. A randomized add-on trial of an N-methyl-D-aspartate antagonist in treatment-resistant bipolar depression. *Archives of General Psychiatry*. 2010 August;67 (8):793-802.
72. Dinan T. Treatment approaches to therapy-resistant depression. *Journal of Psychopharmacology* 1995;9(2 SUPPL.):199-204.
73. Dinan TG. A rational approach to the non-responding depressed patient. *International Clinical Psychopharmacology*. 1993;8(4):221-3.
74. Donohue A. First manic episode in a 55-year-old man after initiation of aripiprazole. *Psychiatry (Edgemont)*. 2010 April;7 (4):37-9.
75. Draper BM. The effectiveness of the treatment of depression in the physically ill elderly. *Aging and Mental Health*. 2000;4(1):9-20.

76. Dresler T, Ehlis AC, Plichta MM, Richter MM, Jabs B, Lesch KP, et al. Panic disorder and a possible treatment approach by means of high-frequency rTMS: A case report. *World Journal of Biological Psychiatry*. 2009;10(4 PART 3):991-7.
77. Dudek D, Siwek M, Borowiecka-Kluza J, Pawlowski T, Kiejna A, Lojko D, et al. q1Bipolar spectrum features in drug resistant unipolar depression patients: TRES-DEP pilot study. *Archives of Psychiatry and Psychotherapy*. 2009 June;11(2):65-73.
78. Dunner D, Kumar R. Paroxetine: A review of clinical experience. *Pharmacopsychiatry*. 1998;31(3):89-101.
79. Dunner DL, Rush AJ, Russell JM, Burke M, Woodard S, Wingard P, et al. Prospective, long-term, multicenter study of the naturalistic outcomes of patients with treatment-resistant depression. *J Clin Psychiatry*. 2006 May;67(5):688-95.
80. Epstein CM, Evatt ML, Funk A, Girard-Siqueira L, Lupei N, Slaughter L, et al. An open study of repetitive transcranial magnetic stimulation in treatment-resistant depression with Parkinson's disease. *Clin Neurophysiol*. 2007 Oct;118(10):2189-94.
81. Eranti S, Mogg A, Pluck G, Landau S, Purvis R, Brown RG, et al. A randomized, controlled trial with 6-month follow-up of repetitive transcranial magnetic stimulation and electroconvulsive therapy for severe depression. *Am J Psychiatry*. 2007 Jan;164(1):73-81.
82. Erdil F, Demirbilek S, Begec Z, Ozturk E, Ersoy MO. Effects of propofol or etomidate on QT interval during electroconvulsive therapy. *Journal of ECT*. 2009 September;25(3):174-7.
83. Etches SM, Schmidt M, Alda M, Hajek T, Kahn DA. Resolution of bipolar II and panic disorders following subarachnoid hemorrhage. *Journal of Psychiatric Practice*. 2009 March;15(2):145-9.
84. Faison WE, Steffens DC. Diagnosis, epidemiology, and clinical course of geriatric depression. *Economics of Neuroscience* 2001;3(7):40-3.
85. Farzan F, Barr MS, Levinson AJ, Chen R, Wong W, Fitzgerald PB, et al. Evidence for gamma inhibition deficits in the dorsolateral prefrontal cortex of patients with schizophrenia. *Brain*. 2010 May;133(5):1505-14.
86. Fava M, Rush AJ, Trivedi MH, Nierenberg AA, Thase ME, Sackeim HA, et al. Background and rationale for the sequenced treatment alternatives to relieve depression (STAR*D) study. *Psychiatric Clinics of North America*. 2003;26(2):457-94.
87. Fawcett J. Why aren't MAOIs used more often? *Journal of Clinical Psychiatry*. 2009 January;70(1):139-40.
88. Fear CF, Littlejohns S, Rouse E, McQuail P. Propofol anaesthesia in electroconvulsive therapy. Reduced seizure duration may not be relevant. *British Journal of Psychiatry*. 1994;165(OCT.):506-9.
89. Feinberg SS. Combining stimulants with monoamine oxidase inhibitors: a review of uses and one possible additional indication. *The Journal of clinical psychiatry*. 2004 Nov;65(11):1520-4.
90. Fenton WS. Evolving perspectives on individual psychotherapy for schizophrenia. *Schizophrenia Bulletin* 2000;26(1):47-72.
91. Fernandez-Llimos F, Tuneu L, Baena MI, Garcia-Delgado A, Faus MJ. Morbidity and mortality associated with pharmacotherapy. Evolution and current concept of drug-related problems. *Current Pharmaceutical Design*. 2004;10(31):3947-67.
92. Ferreri F, Agbokou C, Gauthier S. Recognition and management of neuropsychiatric complications in Parkinson's disease. *Canadian Medical Association Journal* 2006;175(12):1545-52.
93. Ferrucci R, Bortolomasi M, Brunoni A, Vergari M, Tadini L, Giacomuzzi M, et al. Comparative benefits of transcranial direct current stimulation (TDCS) treatment in patients with mild/moderate vs. severe depression. *Clinical Neuropsychiatry*. 2009 December;6(6):246-51.
94. Fiske A, Wetherell JL, Gatz M. Depression in older adults. *General Pathology and Pathological Anatomy*. United States: Annual Reviews Inc. 2009:363-89.

95. Fountoulakis KN, Vieta E. Treatment of bipolar disorder: A systematic review of available data and clinical perspectives. *International Journal of Neuropsychopharmacology* 2008;11(7):999-1029.
96. Franzini A, Messina G, Marras C, Savino M, Miniati M, Bugiani O, et al. Hamilton rating scale for depression-21 modifications in patients with vagal nerve stimulation for treatment of treatment-resistant depression: Series report. *Neuromodulation*. 2008 November;11 (4):267-71.
97. Fu W, Stool LA, White PF, Husain MM. Acute hemodynamic responses to electroconvulsive therapy are not related to the duration of seizure activity. *Journal of Clinical Anesthesia* 1997;9(8):653-7.
98. Fu W, Stool LA, White PF, Husain MM. Is oral clonidine effective in modifying the acute hemodynamic response during electroconvulsive therapy? *Anesth Analg*. 1998;86(5):1127-30.
99. Fugate SE, Ramsey AM. Resistance to oral vitamin K for reversal of overanticoagulation during Crohn's disease relapse. *Journal of Thrombosis and Thrombolysis*. 2004;17(3):219-23.
100. Gabbard GO. How not to teach psychotherapy. *Academic Psychiatry* 2005;29(4):332-8.
101. Gaete JM, Bogousslavsky J. Post-stroke depression. *Expert Review of Neurotherapeutics* 2008;8(1):75-92.
102. Garcia KS, Flynn P, Pierce KJ, Caudle M. Repetitive transcranial magnetic stimulation treats postpartum depression. *Brain Stimulation*. 2010 January;3(1):36-41.
103. Gazdag G, Kocsis N, Tolna J, Ivanyi Z. Etomidate versus propofol for electroconvulsive therapy in patients with schizophrenia. *J ECT*. 2004;20(4):225-9.
104. Gelenberg AJ, Hopkins HS. Report on efficacy of treatments for bipolar disorder. *Psychopharmacology Bulletin* 1993;29(4):447-56.
105. George MS, Rush AJ, Marangell LB, Sackeim HA, Brannan SK, Davis SM, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry*. 2005 Sep 1;58(5):364-73.
106. Ghaemi SN, Schrauwen E, Klugman J, Berv DA, Shirzadi AA, Pardo TB, et al. Long-term lamotrigine plus lithium for bipolar disorder: One year outcome. *Journal of Psychiatric Practice*. 2006;12(5):300-5.
107. Gibson RC, Walcott G. Benzodiazepines for catatonia in persons with schizophrenia and other serious mental illnesses. *Cochrane Database of Systematic Reviews* 2007;-(2).
108. Gibson TB, Jing Y, Carls GS, Kim E, Bagalman JE, Burton WN, et al. Cost burden of treatment resistance in patients with depression. *American Journal of Managed Care*. 2010 May;16(5):370-7.
109. Gieteling M, Hoekstra R, Van Den Broek WW, Bruijn JA. Continuation treatment with electroconvulsive therapy in depression resistant to medication. [Dutch]. *Nederlands Tijdschrift voor Geneeskunde*. 1998;142(38):2110-2.
110. Gill DS, Ketter TA, Post RM. Antidepressant response to sleep deprivation as a function of time into depressive episode in rapidly cycling bipolar patients. *Acta Psychiatrica Scandinavica*. 1993;87 (2):102-9.
111. Ginsberg DL. Low dose oral for selegiline for severe refractory depression. *Primary Psychiatry*. 2006 Jan;13 (1):26-7.
112. Ginsberg DL. Aripiprazole augmentation of clomipramine-refractory obsessive-compulsive disorder. *Primary Psychiatry*. 2007;14(8):19-20.
113. Giovagnoli AR, Villani F, Bell B, Erbetta A, Avanzini G. The chicken with four legs: A case of semantic amnesia and cryptogenic epilepsy. *Epilepsy and Behavior*. 2009 January;14(1):261-8.
114. Goforth HW, Carroll BT. Aripiprazole augmentation of tranylcypromine in treatment-resistant major depression [8]. *Journal of Clinical Psychopharmacology*. 2007 Apr;27 (2):216-7.

115. Goldberg D. The "NICE Guideline" on the treatment of depression. *Epidemiologia e Psichiatria Soc.* 2006;15(1):11-5.
116. Golden RN, Evans DL, Sullivan MD. Antidepressants and tinnitus [2]. *Archives of Internal Medicine.* 1994;154(12).
117. Goodnick PJ, Barrios CA. Use of olanzapine in non-psychotic psychiatric disorders. *Expert Opinion on Pharmacotherapy.* 2001;2(4):667-80.
118. Gormley N. ECT should be treatment option in all cases of refractory depression [7]. *British Medical Journal* 1998;316(7126):233.
119. Gouvea F, Lopes A, Greenberg B, Canteras M, Taub A, Mathis M, et al. Response to sham and active gamma ventral capsulotomy in otherwise intractable obsessive-compulsive disorder. *Stereotactic and Functional Neurosurgery.* 2010 May;88(3):177-82.
120. Grati L, Louzi M, Nasr KB, Zili N, Mansalli L, Mechri A, et al. Compared effects of etomidate and propofol for anaesthesia during electroconvulsive therapy. *Presse Medicale* 2005;34(4):282-4.
121. Greist JH, McElroy. Behavior therapy for obsessive compulsive disorder. *J Clin Psychiatry.* 1994;55(10 SUPPL.):60-8.
122. Grover M, Dorn SD, Weinland SR, Dalton CB, Gaynes BN, Drossman DA. Atypical antipsychotic quetiapine in the management of severe refractory functional gastrointestinal disorders. *Digestive Diseases and Sciences.* 2009 June;54(6):1284-91.
123. Grunhaus L, Dannon PN, Schreiber S, Dolberg OH, Amiaz R, Ziv R, et al. Repetitive transcranial magnetic stimulation is as effective as electroconvulsive therapy in the treatment of nondelusional major depressive disorder: an open study. *Biol Psychiatry.* 2000 Feb 15;47(4):314-24.
124. Grunhaus L, Remen A. Assessment of treatment-resistant major depression - The Michigan adequacy of treatment scale [4]. *Journal of Clinical Psychopharmacology.* 1993;13(3):221-3.
125. Grunhaus L, Schreiber S, Dolberg OT, Polak D, Dannon PN. A randomized controlled comparison of electroconvulsive therapy and repetitive transcranial magnetic stimulation in severe and resistant nonpsychotic major depression. *Biol Psychiatry* 2003:324-31.
126. Guthrie SK, Sung JCY, Goodson J, Grunhaus L, Tandon R. Triazolam and diphenhydramine effects on seizure duration in depressed patients receiving ECT. *Convulsive Therapy.* 1996;12(4):261-5.
127. Hamelin S, Kahane P, Vercueil L. Fatigue in epilepsy: A prospective inter-ictal and post-ictal survey. *Epilepsy Research.* 2010 October;91(2-3):153-60.
128. Hanisch F, Friedemann J, Piro J, Gutmann P. Maintenance electroconvulsive therapy for comorbid pharmacotherapy-refractory obsessive-compulsive and schizoaffective disorder. *European Journal of Medical Research.* 2009 12 Aug;14(8):367-8.
129. Hardy P, Feline A. Refractory depressions. [French]. *Semaine des Hopitaux.* 1988;64(36-37):2421-4.
130. Harris SJ, Parent M. Patient with chronic and apparently treatment-resistant dysthymia. *The American journal of psychiatry.* 1986 Feb;143(2):260-1.
131. Hausmann A, Kemmler G, Walpoth M, Mechtcheriakov S, Kramer-Reinstadler K, Lechner T, et al. No benefit derived from repetitive transcranial magnetic stimulation in depression: A prospective, single centre, randomised, double blind, sham controlled "add on" trial. *Journal of Neurology, Neurosurgery and Psychiatry.* 2004;75(2):320-2.
132. He W, Chai H, Zhang Y, Yu S, Chen W, Wang W. Line bisection performance in patients with generalized anxiety disorder and treatment-resistant depression. *International Journal of Medical Sciences.* 2010;7(4):224-31.
133. Heldt E, Manfro GG, Kipper L, Blaya C, Isolan L, Otto MW. One-year follow-up of pharmacotherapy-resistant patients with panic disorder treated with cognitive-behavior therapy: Outcome and predictors of remission. *Psychotherapy and Psychosomatics* 2006;44(5):657-65.

134. Hermann RC, Ettner SL, Dorwart RA, Langman-Dorwart N, Kleinman S. Diagnoses of patients treated with ECT: A comparison of evidence-based standards with reported use. *Psychiatric Services*. 1999;50(8):1059-65.
135. Hiremani RM, Thirthalli J, Tharayil BS, Gangadhar BN. Double-blind randomized controlled study comparing short-term efficacy of bifrontal and bitemporal electroconvulsive therapy in acute mania. *Bipolar Disorders*. 2008;10(6):701-7.
136. Hirschfeld RMA, Clayton PJ, Cohen I, Fawcett J, Keck P, McClellan J, et al. Practice guideline for the treatment of patients with bipolar disorder. *American Journal of Psychiatry*. 1994;151(12 SUPPL.):1-36.
137. Hixson JD, Kirsch HE. The effects of epilepsy and its treatments on affect and emotion. *Neurocase*. 2009 June;15(3):206-16.
138. Hofmann G, Schony W. Therapy-resistant depressions. [German]. *Psychiatria Danubina*. 1989;1(2):131-4.
139. Hornby AP, Sharma M, Stegman B. Standardized natural product cannabis in pain management and observations at a Canadian compassion society: A case report. *Cases Journal*. 2009 May;2 (5)(7487).
140. Hrdlicka M, Blatny M, Urbanek T, Moran M, Manasova I. Electroconvulsive therapy: Does a history of pharmacoresistance influence the therapeutic response?. [Czech]. *Ceska a Slovenska Psychiatrie*. 2001;97(2):56-9.
141. Hupfeld Moreno D, Moreno RA. Resistant depressions: Treatment approach. [Portuguese]. *Jornal Brasileiro de Psiquiatria*. 1993;42(SUPPL. 1).
142. Iosifescu DV, Bankier B, Fava M. Impact of medical comorbid disease on antidepressant treatment of major depressive disorder. *Current Psychiatry Reports*. 2004;6(3):193-201.
143. Ivanyi Z, Tolna J, Gazdag G. Impact of propofol and etomidate on seizure activity during electroconvulsive therapy in patients with schizophrenia [59]. *Anesthesia and Analgesia*. 2007;104(1):241.
144. Jakovljevic M, Filakovic P, Ljubicic D. Die Behandlung Der Gegen Ubliche Psychopharmakotherapie Resistenten Affektiven Storungen. *Psychiatria Danubina*. 1992;4(1-2):119-26.
145. Janakiramaiah N, Motreja S, Gangadhar BN, Subbakrishna DK, Parameshwara G. Once vs. three times weekly ECT in melancholia: A randomized controlled trial. *Acta Psychiatrica Scandinavica*. 1998;98(4):316-20.
146. Jenike MA. Pharmacologic treatment of obsessive compulsive disorders. *Psychiatric Clinics of North America*. 1992;15(4):895-919.
147. Jenike MA. Psychiatric illnesses in the elderly: A review. *Journal of Geriatric Psychiatry and Neurology*. 1996;9(2):57-82.
148. Jeronimo A, Meira C, Amaro A, Campello GC, Granja C. Cardiogenic shock caused by disulfiram. [Spanish, Portuguese, English]. *Arquivos Brasileiros de Cardiologia*. 2009 March;92 (3):e16-e8.
149. Jurysta F, Kempnaers C, Lancini J, Lanquart JP, Van De Borne P, Linkowski P. Altered interaction between cardiac vagal influence and delta sleep EEG suggests an altered neuroplasticity in patients suffering from major depressive disorder: Brief communication. *Acta Psychiatrica Scandinavica*. 2010 March;121(3):236-9.
150. Kafantaris V. Treatment of bipolar disorder in children and adolescents. *Journal of the American Academy of Child and Adolescent Psychiatry*. 1995;34(6):732-41.
151. Kahn DA, Sachs GS, Printz DJ, Carpenter D, Docherty JP, Ross R. Expert consensus guidelines for the medication treatment of bipolar disorder: A new treatment tool. *Postgrad Med*. 2001;3(1):49-57.
152. Kapfhamer J, Russeth K, Heinrich T. Subcutaneous injection of intranasal canine kennel cough vaccine. *Psychosomatics*. 2009 March-April;50 (2):180.
153. Kapural L, Lokey K, Leong MS, Fiekowsky S, Stanton-Hicks M, Sapienza-Crawford AJ, et al. Intrathecal ziconotide for complex regional pain syndrome: Seven case reports. *Pain Practice*. 2009;9 (4):296-303.

154. Kaufman CB, Mink JW, Schwalb JM. Bilateral deep brain stimulation for treatment of medically refractory paroxysmal nonkinesigenic dyskinesia. *Journal of Neurosurgery*. 2010 April;112(4):847-50.
155. Kerrigan F. Antidepressant patents: 1995-1997. *Expert Opinion on Therapeutic Patents*. 1998;8(4):439-60.
156. Kessler U, Vaaler AE, Schoyen H, Oedegaard KJ, Bergsholm P, Andreassen OA, et al. The study protocol of the Norwegian randomized controlled trial of electroconvulsive therapy in treatment resistant depression in bipolar disorder. *BMC Psychiatry*. 2010;10:16.
157. Khalid I, Rana L, Khalid TJ, Roehrs T. Refractory restless legs syndrome likely caused by olanzapine. *Journal of Clinical Sleep Medicine*. 2009 15 Feb;5(1):68-9.
158. Khan A, Mirolo MH, Lai H, Claypoole K, Bierut L, Malik R, et al. ECT and TRH: Cholinergic involvement in a cognitive deficit state. *Psychopharmacology Bulletin* 1993;29(3):345-52.
159. Kimmel PL, Levy N, Vassalotti J, Christensen A, Friend R, Veis J, et al. Psychosocial factors in dialysis patients. *Kidney International*. 2001;59(4):1599-613.
160. Kivela SL. Treatment of depressive disorders in old age. *Current Opinion in Psychiatry* 2001;14(4):387-93.
161. Kojima H, Terao T, Yoshimura R. Serotonin syndrome during clomipramine and lithium treatment [1]. *American Journal of Psychiatry*. 1993;150(12).
162. Kok RM, Nolen WA, Heeren TJ. Outcome of late-life depression after 3 years of sequential treatment. *Acta Psychiatrica Scandinavica*. 2009;119(4):274-81.
163. Kok RM, Van Maarschalkerweerd WWA. Treatment resistant depression in the elderly; when is it inadvisable to prescribe tricyclic antidepressants?. [Dutch]. *Tijdschrift voor Psychiatrie*. 2004;46(11):769-73.
164. Kuba R, Novotna I, Brazdil M, Kocvarova J, Tyrlikova I, Mastik J, et al. Long-term levetiracetam treatment in patients with epilepsy: 3-year follow up. *Acta Neurologica Scandinavica*. 2010 February;121(2):83-8.
165. Kubera M, Maes M, Budziszewska B, Basta-Kaim A, Leskiewicz M, Grygier B, et al. Inhibitory effects of amantadine on the production of pro-inflammatory cytokines by stimulated in vitro human blood. *Pharmacological Reports*. 2009;61(6):1105-12.
166. Kucia KA, Stepanczak R, Tredzbor B. Electroconvulsive therapy for major depression in an elderly person with epilepsy. *World Journal of Biological Psychiatry*. 2009;10(1):78-80.
167. Kuehnert MJ, Webb RM, Jochimsen EM, Hancock GA, Arduino MJ, Hand S, et al. Staphylococcus aureus bloodstream infections among patients undergoing electroconvulsive therapy traced to breaks in infection control and possible extrinsic contamination by propofol. *Anesthesia and Analgesia*. 1997;85(2):420-5.
168. Lai CH. Mirtazapine and Bupropion Combined Treatment in Treatment-resistant Depression. *Tzu Chi Medical Journal*. 2009 December;21(4):352-4.
169. Leftheriotis D, Flevari P, Ikonomidis I, Douzenis A, Liapis C, Paraskevaidis I, et al. The role of the selective serotonin re-uptake inhibitor sertraline in nondepressive patients with chronic ischemic heart failure: A preliminary study. *PACE - Pacing and Clinical Electrophysiology*. 2010 October;33(10):1217-23.
170. Leon AC, Hedeker D. A comparison of mixed-effects quantile stratification propensity adjustment strategies for longitudinal treatment effectiveness analyses of continuous outcomes. *Statistics in Medicine*. 2007;26(13):2650-65.
171. Levene M. Recognition and management of neonatal seizures. *Paediatrics and Child Health*. 2008;18(4):178-82.
172. Levine J, Mishori A, Susnosky M, Martin M, Belmaker RH. Combination of inositol and serotonin reuptake inhibitors in the treatment of depression. *Biological Psychiatry*. 1999;45(3):270-3.

173. Levkovitz Y, Harel EV, Roth Y, Braw Y, Most D, Katz LN, et al. Deep transcranial magnetic stimulation over the prefrontal cortex: Evaluation of antidepressant and cognitive effects in depressive patients. *Brain Stimulation*. 2009 October;2(4):188-200.
174. Levy ML, Levy KM, Hoff D, Amar AP, Park MS, Conklin JM, et al. Vagus nerve stimulation therapy in patients with autism spectrum disorder and intractable epilepsy: Results from the vagus nerve stimulation therapy patient outcome registry - Clinical article. *Journal of Neurosurgery: Pediatrics*. 2010 June;5(6):595-602.
175. Licht CMM, De Geus EJC, Van Dyck R, Penninx BWJH. Longitudinal evidence for unfavorable effects of antidepressants on heart rate variability. *Biological Psychiatry*. 2010;68 (9):861-8.
176. Licht RW, Gijsman H, Nolen WA, Angst J. Are antidepressants safe in the treatment of bipolar depression? A critical evaluation of their potential risk to induce switch into mania or cycle acceleration. *Acta Psychiatrica Scandinavica*. 2008;118(5):337-46.
177. Licht RW, Vestergaard P, Brodersen A. Long-term outcome of patients with bipolar disorder commenced on lithium prophylaxis during hospitalization: A complete 15-year register-based follow-up. *Bipolar Disorders*. 2008;10(1):79-86.
178. Lieberman A. An integrated approach to patient management in Parkinson's disease. *Neurologic Clinics*. 1992;10(2):553-65.
179. Lieberman JA, Greenhouse J, Hamer RM, Krishnan KR, Nemeroff CB, Sheehan DV, et al. Comparing the effects of antidepressants: Consensus guidelines for evaluating quantitative reviews of antidepressant efficacy. *Neuropsychopharmacology*. 2005;30(3):445-60.
180. Lindenmayer JP, Alcantara F, Khan A, Ciranni M. The effects of molindone as a concomitant medication on aggressive behavior. *Clinical Schizophrenia and Related Psychoses*. 2010 01 Jan;3 (4):193-200.
181. Lisanby SH, Luber B, Schlaepfer TE, Sackeim HA. Safety and feasibility of magnetic seizure therapy (MST) in major depression: randomized within-subject comparison with electroconvulsive therapy. *Neuropsychopharmacology*. 2003 Oct;28(10):1852-65.
182. Little JT, Reynolds ICF, Dew MA, Frank E, Begley AE, Miller MD, et al. How common is resistance to treatment in recurrent, nonpsychotic geriatric depression? *American Journal of Psychiatry*. 1998;155(8):1035-8.
183. Loo C, Martin D, Pigot M, Arul-Anandam P, Mitchell P, Sachdev P. Transcranial direct current stimulation priming of therapeutic repetitive transcranial magnetic stimulation: A pilot study. *Journal of ECT*. 2009 December;25(4):256-60.
184. Loo CK, Kaill A, Paton P, Simpson B. The difficult-to-treat electroconvulsive therapy patient - Strategies for augmenting outcomes. *Journal of affective disorders*. 2010 August;124 (3):219-27.
185. Machado-Vieira R, Soares JC. Treatment-resistant mood disorders. [Portuguese, English]. *Revista Brasileira de Psiquiatria*. 2007;29(SUPPL. 2):S48-S54.
186. Maes M. "Functional" or "psychosomatic" symptoms, e.g. a flu-like malaise, aches and pain and fatigue, are major features of major and in particular of melancholic depression. *Neuroendocrinology Letters*. 2009;30 (5):564-73.
187. Maizels M. Clonazepam for refractory headache: Three cases illustrative of benefit and risk. *Headache*. 2010 April;50 (4):650-6.
188. Malison RT, Anand A, Pelton GH, Kirwin P, Carpenter L, McDougale CJ, et al. Limited efficacy of ketoconazole in treatment-refractory major depression. *Journal of Clinical Psychopharmacology*. 1999;19(5):466-70.
189. Mantovani A, Lisanby SH, Pieraccini F, Ulivelli M, Castrogiovanni P, Rossi S. Repetitive Transcranial Magnetic Stimulation (rTMS) in the treatment of panic disorder (PD) with comorbid major depression. *J Affect Disord*. 2007 Sep;102(1-3):277-80.

190. Martin-Blanco A, Pascual JC, Soler J, Valdeperez A, Perez V. Quetiapine in the treatment of refractory irritable bowel syndrome. A case report. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2010 May;34 (4):715-6.
191. Massol J, Martin P, Belon JP, Puech AJ, Soubrie P. Helpless behavior (escape deficits) in streptozotocin-diabetic rats: Resistance to antidepressant drugs. *Psychoneuroendocrinology*. 1989;14(1-2):145-53.
192. Mayur PM, Shree RS, Gangadhar BN, Subbakrishna DK, Janakiramaiah N, Rao GSU. Atropine premedication and the cardiovascular response to electroconvulsive therapy. *British Journal of Anaesthesia*. 1998;81(3):466-7.
193. Mazeh D, Melamed Y, Elizur A. Venlafaxine in the treatment of resistant postpsychotic depressive symptoms of schizophrenia [8]. *Journal of Clinical Psychopharmacology*. 1999;19(3):284-5.
194. Mazza M, Di Nicola M, Martinotti G, Taranto C, Janiri L, Brija P, et al. Treatment of schizophrenia. *Minerva Psichiatrica*. 2007;48(1):43-53.
195. McCall WV, Farah BA, Reboussin D, Colenda CC. Comparison of the efficacy of titrated, moderate-dose and fixed, high-dose right unilateral ECT in elderly patients. *American Journal of Geriatric Psychiatry*. 1995;3(4):317-24.
196. McCall WV, Sparks W, Jane J, Rosenquist PB, Colenda CC, Reboussin DM. Variation of ictal electroencephalographic regularity with low-, moderate-, and high-dose stimuli during right unilateral electroconvulsive therapy. *Biological Psychiatry*. 1998;43(8):608-11.
197. McCormick LM, Brumm MC, Benede AK, Lewis JL. Relative ineffectiveness of ultrabrief right unilateral versus bilateral electroconvulsive therapy in depression. *Journal of ECT*. 2009 December;25(4):238-42.
198. McNamara B, Ray JL, Arthurs OJ, Boniface S. Transcranial magnetic stimulation for depression and other psychiatric disorders. *Psychological Medicine*. 2001;31(7):1141-6.
199. Mhalla A, de Andrade DC, Baudic S, Perrot S, Bouhassira D. Alteration of cortical excitability in patients with fibromyalgia. *Pain*. 2010 June;149(3):495-500.
200. Minelli A, Bortolomasi M, Scassellati C, Salvoro B, Avesani M, Manganotti P. Effects of intravenous antidepressant drugs on the excitability of human motor cortex: a study with paired magnetic stimulation on depressed patients. *Brain Stimulation*. 2010 January;3(1):15-21.
201. Mingli H, Zhengtian G, Xinyi W, Xiaoping T. Effects of repetitive transcranial magnetic stimulation on hypothalamic-pituitary-adrenal axis of patients with depression. *Journal of Medical Colleges of PLA*. 2009 December;24(6):337-45.
202. Mitchell PB. Management of treatment-resistant depression in the late 1990s. *Hong Kong Journal of Psychiatry*. 1999;9(1):3-11.
203. Mizrak A, Koruk S, Ganidagli S, Bulut M, Oner U. Premedication with dexmedetomidine and midazolam attenuates agitation after electroconvulsive therapy. *Journal of Anesthesia*. 2009;23(1):6-10.
204. Mogg A, Pluck G, Eranti SV, Landau S, Purvis R, Brown RG, et al. A randomized controlled trial with 4-month follow-up of adjunctive repetitive transcranial magnetic stimulation of the left prefrontal cortex for depression. *Psychol Med*. 2008 Mar;38(3):323-33.
205. Mohan TSP, Tharyan P, Alexander J, Raveendran NS. Effects of stimulus intensity on the efficacy and safety of twice-weekly, bilateral electroconvulsive therapy (ECT) combined with antipsychotics in acute mania: A randomised controlled trial. *Bipolar Disorders*. 2009;11(2):126-34.
206. Morgan PT. Treatment-resistant depression: Response to low-dose transdermal but not oral selegiline [10]. *Journal of Clinical Psychopharmacology*. 2007 Jun;27 (3):313-4.
207. Morra E, Lazzarino M, Alimena G, Liberati AM, Grignani F, Mandelli F, et al. The role of interferon in the treatment of chronic myelogenous leukemia: Results and prospects. *Leukemia and Lymphoma*. 1992;6(4-5):305-15.

208. Mufti MA, Holtzheimer IPE, Epstein CM, Quinn SC, Vito N, McDonald WM. Bupropion decreases resting motor threshold: A case report. *Brain Stimulation*. 2010;3 (3):177-80.
209. Mulder RT, Joyce PR, Frampton CMA. Personality disorders improve in patients treated for major depression. *Acta Psychiatrica Scandinavica*. 2010 September;122 (3):219-25.
210. Muller H, Demling JH, Schutz P, Weigel D, Kornhuber J, Sperling W. Safety of vagus nerve stimulation in a patient with bipolar disorder and an implanted cardioverter-defibrillator. *Acta Neurologica Scandinavica*. 2010 April;121(4):285-6.
211. Muller N. Tourette's syndrome: Clinical features, pathophysiology, and therapeutic approaches. *Dialogues in Clinical Neuroscience*. 2007;9(2):161-71.
212. Munk-Olsen T, Laursen TM, Videbech P, Mortensen PB, Rosenberg R. All-cause mortality among recipients of electroconvulsive therapy: Register-based cohort study. *British Journal of Psychiatry*. 2007;190(MAY):435-9.
213. Murray G, Michalak EE, Axler A, Yaxley D, Hayashi B, Westrin A, et al. Relief of Chronic or Resistant Depression (Re-ChORD): A pragmatic, randomized, open-treatment trial of an integrative program intervention for chronic depression. *Journal of Affective Disorders*. 2010 June;123(1-3):243-8.
214. Myers A, Barrueto Jr F. Refractory priapism associated with ingestion of yohimbe extract. *Journal of Medical Toxicology*. 2009;5 (4):223-5.
215. Nahas Z, Kozel FA, Li X, Anderson B, George MS. Left prefrontal transcranial magnetic stimulation (TMS) treatment of depression in bipolar affective disorder: a pilot study of acute safety and efficacy. *Bipolar Disord*. 2003 Feb;5(1):40-7.
216. Naz B, Craig TJ, Bromet EJ, Finch SJ, Fochtmann LJ, Carlson GA. Remission and relapse after the first hospital admission in psychotic depression: A 4-year naturalistic follow-up. *Psychological Medicine*. 2007;37(8):1173-81.
217. Ng B. The role of psychostimulants in psychogeriatrics: A New Zealand survey. *Psychogeriatrics*. 2009 September;9 (3):121-6.
218. Nguyen TT, Chhibber AK, Lustik SJ, Kolano JW, Dillon PJ, Guttmacher LB. Effect of methohexitone and propofol with or without alfentanil on seizure duration and recovery in electroconvulsive therapy. *British Journal of Anaesthesia*. 1997;79(6):801-3.
219. Nierenberg AA. Low-dose buspirone, melatonin and low-dose bupropion added to mood stabilizers for severe treatment-resistant bipolar depression. *Psychotherapy and Psychosomatics*. 2009;78 (6):391-3.
220. Nierenberg AA, Trivedi MH, Gaynes BN, Mitchell J, Davis LL, Husain MM, et al. Effectiveness study of venlafaxine-XR combined with aripiprazole for chronic or recurrent major depressive disorder. *Australian and New Zealand Journal of Psychiatry*. 2009;43 (10):956-67.
221. Nikolajsen L, Jensen TS. Phantom limb pain. *British Journal of Anaesthesia*. 2001;87(1):107-16.
222. Nolen WA, Van Den Broek WW, Birkenhager TK. Treatment with low doses of tranlycypromine resulted in a disappointing remission rate [1]. *American Journal of Psychiatry* 2007;164(3):524.
223. Nomoto K, Suzuki T, Serada K, Oe K, Yoshida T, Yamada S. Effects of landiolol on hemodynamic response and seizure duration during electroconvulsive therapy. *Journal of Anesthesia*. 2006;20(3):183-7.
224. O'Connor MG, Jerskey BA, Robertson EM, Brenninkmeyer C, Ozdemir E, Leone AP. The effects of repetitive transcranial magnetic stimulation (rTMS) on procedural memory and dysphoric mood in patients with major depressive disorder. *Cogn Behav Neurol*. 2005 Dec;18(4):223-7.
225. Ogawa S, Okutani R, Suehiro K, Shigemoto T. Refractory hypotension during remifentanil-based anesthesia in a patient receiving long-term antidepressant therapy. *Anesthesia and Resuscitation*. 2009 March;45 (1):27-9.

226. Okabe S, Ugawa Y, Kanazawa I. 0.2-Hz repetitive transcranial magnetic stimulation has no add-on effects as compared to a realistic sham stimulation in parkinson's disease. *Movement Disorders*. 2003;18(4):382-8.
227. Okamoto H, Shimizu E, Ozawa K, Hashimoto K, Iyo M. Lithium augmentation in milnacipran-refractory depression for the prevention of relapse following electroconvulsive therapy [1]. *Australian and New Zealand Journal of Psychiatry*. 2005 Jan;39 (1-2):108.
228. Okay T, Sengul C, Gulunay A, Sengul CB, Erken DD, Dilbaz N. The short term effects of naproxen sodium on treatment satisfaction and headache as a side-effect of electroconvulsive therapy: A preliminary study. *Klinik Psikofarmakoloji Bulteni*. 2008;18(1):41-5.
229. O'Leary D, Gill D, Gregory S, Shawcross C. Which depressed patients respond to ECT? The Nottingham results. *Journal of Affective Disorders* 1995;33(4):245-50.
230. Ordas DM, Ritchie EC. Treatment of depersonalization disorder and associated depression with electroconvulsive therapy [8]. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1994;6(1):67-9.
231. Osser DN. A systematic approach to the classification and pharmacotherapy of nonpsychotic major depression and dysthymia. *Journal of Clinical Psychopharmacology*. 1993;13(2):133-44.
232. Otsuka T, Togo T, Sugiyama N, Uehara K, Yoshimi A, Karashima A, et al. Perospirone augmentation of paroxetine in treatment of refractory obsessive-compulsive disorder with depression. *Progress in Neuro-Psychopharmacology and Biological Psychiatry*. 2007 30 Mar;31 (2):564-6.
233. Ottaviani C, Shapiro D, Davydov DM, Goldstein IB, Mills PJ. The autonomic phenotype of rumination. *International Journal of Psychophysiology*. 2009 June;72(3):267-75.
234. Otter M, Cohen D. Electroconvulsive therapy in depressed adolescent [3]. *Nederlands Tijdschrift voor Geneeskunde*. 2007;151(47):2643-4.
235. Ozcan ME, Suppes T. Methyltestosterone add-on in bipolar depression: A case report. *Klinik Psikofarmakoloji Bulteni*. 2009;19 (SUPPL. 1):S166-S7.
236. Paillere Martinot ML, Galinowski A, Ringuenet D, Gallarda T, Lefaucheur JP, Bellivier F, et al. Influence of prefrontal target region on the efficacy of repetitive transcranial magnetic stimulation in patients with medication-resistant depression: A [18F]-fluorodeoxyglucose PET and MRI study. *International Journal of Neuropsychopharmacology* 2010:45-59.
237. Pal E, Nagy F, Aschermann Z, Balazs E, Kovacs N. The impact of left prefrontal repetitive transcranial magnetic stimulation on depression in Parkinson's disease: A randomized, double-blind, placebo-controlled study. *Movement Disorders*. 2010 October;25 (14):2311-7.
238. Palm U, Keeser D, Schiller C, Fintescu Z, Reisinger E, Baghai TC, et al. Transcranial direct current stimulation in a patient with therapy-resistant major depression. *World Journal of Biological Psychiatry*. 2009;10(4 PART 2):632-5.
239. Pancheri P. Guide of pharmacological treatment of depression. Consensus Conference - Firenze, 24-25 September 1993. [Italian]. *Rivista di Psichiatria*. 1994;29(5):257-77.
240. Pantelis C, Barnes TRE. Drug strategies and treatment-resistant schizophrenia. *Australian and New Zealand Journal of Psychiatry*. 1996;30(1):20-37.
241. Parker G, Malhi G. Are atypical antipsychotic drugs also atypical antidepressants? *Australian and New Zealand Journal of Psychiatry*. 2001;35(5):631-8.
242. Parsa MA, Simon M, Dubrow C, Ramirez LF, Meltzer HY. Psychiatric manifestations of olivo-ponto-cerebellar atrophy and treatment with clozapine. *International Journal of Psychiatry in Medicine*. 1993;23 (2):149-56.
243. Partonen T, Sihvo S, Lonnqvist JK. Patients excluded from an antidepressant efficacy trial. *Journal of Clinical Psychiatry*. 1996;57(12):572-5.

244. Patkar AA, Peindl K, Mago R, Mannelli P, Masand PS. An open-label, rater-blinded, augmentation study of aripiprazole in treatment-resistant depression. *Primary Care Companion to the Journal of Clinical Psychiatry*. 2006;8 (2):82-7.
245. Paul R, Schaaff N, Padberg F, Moller HJ, Frodl T. Comparison of racemic ketamine and S-ketamine in treatment-resistant major depression: Report of two cases. *World Journal of Biological Psychiatry*. 2009;10 (3):241-4.
246. Peet M, Pratt JP. Lithium - Current status in psychiatric disorders. *Drugs*. 1993;46(1):7-17.
247. Pereira EAC, Wang S, Paterson DJ, Stein JF, Aziz TZ, Green AL. Sustained reduction of hypertension by deep brain stimulation. *Journal of Clinical Neuroscience*. 2010 January;17 (1):124-7.
248. Petrides G, Braga RJ, Fink M, Mueller M, Knapp R, Husain M, et al. Seizure threshold in a large sample: Implications for stimulus dosing strategies in bilateral electroconvulsive therapy: A report from core. *Journal of ECT*. 2009 December;25(4):232-7.
249. Petrides G, Fink M. The 'half-age' stimulation strategy for ECT dosing. *Convulsive Therapy*. 1996;12(3):138-46.
250. Pierog JE, Kane KE, Kane BG, Donovan JW, Helmick T. Tricyclic antidepressant toxicity treated with massive sodium bicarbonate. *American Journal of Emergency Medicine*. 2009 November;27 (9):1168.e3-.e7.
251. Post RM, Leverich GS, Altshuler L, Mikalaukas K. Lithium-discontinuation-induced refractoriness: Preliminary observations. *American Journal of Psychiatry*. 1992;149(12):1727-9.
252. Poutanen O, Huuhka K, Perko K. Severe anorexia nervosa, co-occurring major depressive disorder and electroconvulsive therapy as maintenance treatment: A case report. *Cases Journal*. 2009 December;2 (12)(9362).
253. Prahara SK, Ram D, Arora M. Efficacy of high frequency (rapid) suprathreshold repetitive transcranial magnetic stimulation of right prefrontal cortex in bipolar mania: A randomized sham controlled study. *Journal of Affective Disorders*. 2009 October;117(3):146-50.
254. Pratap R, Farboud A, Patel H, Montgomery P. Vagal nerve stimulator implantation: The otolaryngologist's perspective. *European Archives of Oto-Rhino-Laryngology*. 2009 September;266(9):1455-9.
255. Price RB, Nock MK, Charney DS, Mathew SJ. Effects of Intravenous Ketamine on Explicit and Implicit Measures of Suicidality in Treatment-Resistant Depression. *Biological Psychiatry*. 2009 01 Sep;66 (5):522-6.
256. Proietti Cecchini A, Mea E, Tullo V, Curone M, Franzini A, Broggi G, et al. Vagus nerve stimulation in drug-resistant daily chronic migraine with depression: Preliminary data. *Neurological Sciences*. 2009;30(SUPPL. 1):S101-S4.
257. Prudic J, Sackeim HA. Electroconvulsive therapy suicide risk. *Journal of Clinical Psychiatry*. 1999;60(SUPPL. 2):104-10.
258. Puigdemont D, Portella MJ, Perez-Egea R, de Diego-Adelino J, Gironell A, Molet J, et al. Depressive Relapse After Initial Response to Subcallosal Cingulate Gyrus-Deep Brain Stimulation in a Patient with a Treatment-Resistant Depression: Electroconvulsive Therapy as a Feasible Strategy. *Biological Psychiatry*. 2009 01 Sep;66 (5):e11-e2.
259. Puzynski S, Koszewska I, Kalinowski A, Bogdanowicz E, Swiecicki L. Drug-resistance in endogenous depression. Part II. Refractoriness to antidepressants in the course of affective disorders. [Polish]. *Psychiatria Polska*. 1994;28(1):5-15.
260. Rabinak CA, Nirenberg MJ. Dopamine agonist withdrawal syndrome in parkinson disease. *Archives of Neurology*. 2010 January;67 (1):58-63.
261. Rachid F, Golaz J, Bondolfi G, Bertschy G. Induction of a mixed depressive episode during rTMS treatment in a patient with refractory major depression. *World Journal of Biological Psychiatry*. 2006;7(4):261-4.

262. Radzik J, Zawadzka A, Leszek J, Mis M, Druszcz A. The course of meningioma of the olfactory groove in a patient with a 7-year long psychiatric history: Case study, and diagnostic difficulties. *Psychogeriatría Polska*. 2009;6 (3):135-9.
263. Raes F, Sienaert P, Demyttenaere K, Peuskens J, Williams JMG, Hermans D. Overgeneral memory predicts stability of short-term outcome of electroconvulsive therapy for depression. *Journal of ECT*. 2008;24(1):81-3.
264. Rane LJ, Fekadu A, Wooderson S, Poon L, Markopoulou K, Cleare AJ. Discrepancy between subjective and objective severity in treatment-resistant depression: Prediction of treatment outcome. *Journal of Psychiatric Research*. 2010 November;44 (15):1082-7.
265. Rasmussen KG. Electroconvulsive therapy versus transcranial magnetic stimulation for major depression: A review with recommendations for future research. *Acta Neuropsychiatrica*. 2008;20(6):291-4.
266. Rasmussen KG, Laurila DR, Brady BM, Lewis CL, Niemeyer KD, Sun NM, et al. Seizure length with sevoflurane and thiopental for induction of general anesthesia in electroconvulsive therapy: A randomized double-blind trial. *Journal of ECT*. 2006;22(4):240-2.
267. Rasmussen KG, Laurila DR, Brady BM, Lewis CL, Niemeyer KD, Sun NM, et al. Anesthesia outcomes in a randomized double-blind trial of sevoflurane and thiopental for induction of general anesthesia in electroconvulsive therapy. *Journal of ECT*. 2007;23(4):236-8.
268. Rasmussen KG, Mueller M, Knapp RG, Husain MM, Rummans TA, Sampson SM, et al. Antidepressant medication treatment failure does not predict lower remission with ECT for major depressive disorder: A report from the consortium for research in electroconvulsive therapy. *J Clin Psychiatry*. 2007;68(11):1701-6.
269. Reus VI. Rational polypharmacy in the treatment of mood disorders. *Annals of Clinical Psychiatry*. 1993;5(2):91-100.
270. Rohan M, Parow A, Stoll AL, Demopoulos C, Friedman S, Dager S, et al. Low-field magnetic stimulation in bipolar depression using an MRI-based stimulator. *American Journal of Psychiatry*. 2004;161(1):93-8.
271. Rosa MA, Rosa MO, Belegarde IMT, Bueno CR, Fregni F. Recovery after ECT: comparison of propofol, etomidate and thiopental. *Revista Brasileira de Psiquiatria*. 2008;30(2):149-51.
272. Rosan TA, Mesones HL, Brengio F. Combined therapy with tricyclic and MAOI antidepressants in the treatment of resistant major depression. [Spanish]. *Acta Psiquiátrica y Psicológica de América Latina*. 1994;40(4):314-20.
273. Rosche J, Uhlmann C, Weber R. Changes of Coping Strategies in Patients with Therapy Refractory Epilepsy in the Course of a Ward Based Treatment with a Holistic Therapeutic Approach. [German]. *PPmP Psychotherapie Psychosomatik Medizinische Psychologie*. 2004;54(1):4-8.
274. Rosenberg O, Shoenfeld N, Kotler M, Dannon PN. Mood disorders in elderly population: Neurostimulative treatment possibilities. *Recent Patents on CNS Drug Discovery*. 2009;4(2):149-55.
275. Rosenberg O, Shoenfeld N, Zangen A, Kotler M, Dannon PN. Deep TMS in a resistant major depressive disorder: A brief report. *Depression and Anxiety*. 2010 May;27(5):465-9.
276. Rosenberg PB, Mehndiratta RB, Mehndiratta YP, Wamer A, Rosse RB, Balish M. Repetitive transcranial magnetic stimulation treatment of comorbid posttraumatic stress disorder and major depression. *J Neuropsychiatry Clin Neurosci*. 2002 Summer;14(3):270-6.
277. Rosenlicht NZ, Gerner RH. Systematic approach to the psychopharmacologic treatment of resistant depression. *Annals of Clinical Psychiatry*. 1990;2(1):57-65.
278. Rosenquist PB, McCall WV, Farah A, Reboussin DM. Effects of caffeine pretreatment on measures of seizure impact. *Convulsive Therapy*. 1994;10(2):181-5.

279. Rossi S, Ulivelli M, Malentacchi M, Greco G, Bartalini S, Borgogni P, et al. Effects of immunotherapy on motor cortex excitability in Stiff Person Syndrome. *Journal of Neurology*. 2010 February;257(2):281-5.
280. Roth RM, Jobst BC, Thadani VM, Gilbert KL, Roberts DW. New-onset obsessive-compulsive disorder following neurosurgery for medication-refractory seizure disorder. *Epilepsy and Behavior*. 2009 April;14(4):677-80.
281. Rucklidge JJ. Successful treatment of OCD with a micronutrient formula following partial response to Cognitive Behavioral Therapy (CBT): A case study. *Journal of Anxiety Disorders*. 2009;23(6):836-40.
282. Sackeim HA, Prudic J, Devanand DP, Nobler MS, Lisanby SH, Peyser S, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry*. 2000;57(5):425-34.
283. Sackeim HA, Prudic J, Nobler MS, Fitzsimons L, Lisanby SH, Payne N, et al. Effects of pulse width and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *Brain Stimulation*. 2008;1(2):71-83.
284. Sadrediny S, Molaeeaphard M, Mir-Ahmadi M. Sexual disorder improvement: A target or a way in treatment of fibromyalgia. A case report and brief review. *Modern Rheumatology*. 2010 February;20(1):74-6.
285. Saito S, Kadoi Y, Nara T, Sudo M, Obata H, Morita T, et al. The comparative effects of propofol versus thiopental on middle cerebral artery blood flow velocity during electroconvulsive therapy. *Anesth Analg*. 2000;91(6):1531-6.
286. Saitoh A, Yamaguchi K, Murasawa H, Kamei J. The approaches in the discovery of antidepressants using affective disorder models. [Japanese]. *Japanese Journal of Neuropsychopharmacology*. 2003;23(2):75-82.
287. Sajatovic M, Gyulai L, Calabrese JR, Thompson TR, Wilson BG, White R, et al. Maintenance treatment outcomes in older patients with bipolar I disorder. *American Journal of Geriatric Psychiatry*. 2005;13(4):305-11.
288. Sakkas P, Theleritis CG, Psarros C, Papadimitriou GN, Soldatos CR. Jacksonian seizure in a manic patient treated with rTMS. *World Journal of Biological Psychiatry*. 2008;9(2):159-60.
289. Saldana MT, Navarro A, Perez C, Masramon X, Rejas J. Patient-reported-outcomes in subjects with painful lumbar or cervical radiculopathy treated with pregabalin: Evidence from medical practice in primary care settings. *Rheumatology International*. 2010 June;30(8):1005-15.
290. Samaras N, Rossi G, Giannakopoulos P, Gold G. Vascular depression. An age-related mood disorder. *European Geriatric Medicine*. 2010;1(4):220-5.
291. Sampson SM, Rome JD, Rummans TA. Slow-frequency rTMS reduces fibromyalgia pain. *Pain Med*. 2006 Mar-Apr;7(2):115-8.
292. Santos MA, Hara C, Stumpf BLP, Rocha FL. Treatment-resistant depression: Review of pharmacologic antidepressant strategies. *Jornal Brasileiro de Psiquiatria*. 2006;55(3):232-42.
293. Santy PA, Bryant SG. Teaching clinical psychopharmacology on an inpatient psychiatric research center. *Journal of Clinical Pharmacology*. 1994;34(3):215-21.
294. Satterthwaite TD, Cristancho MA, Alici Y, Weiss D, O'Reardon JP. Electroconvulsive therapy in a 72-year-old woman with a history of Takotsubo cardiomyopathy: a case report and review of the literature. *Brain Stimulation*. 2009 October;2(4):238-40.
295. Schaffer A, Levitt AJ, Joffe RT. Mexiletine in treatment-resistant bipolar disorder. *Journal of affective disorders*. 2000 Jan;57(1-3):249-53.
296. Schiffer F, Teicher MH, Anderson C, Tomoda A, Polcari A, Navalta CP, et al. Determination of hemispheric emotional valence in individual subjects: A new approach with research and therapeutic implications. *Behavioral and Brain Functions*. 2007;3(-).

297. Schmidt EZ, Reininghaus B, Enzinger C, Ebner C, Hofmann P, Kapfhammer HP. Changes in brain metabolism after ECT-Positron emission tomography in the assessment of changes in glucose metabolism subsequent to electroconvulsive therapy - Lessons, limitations and future applications. *Journal of Affective Disorders*. 2008;106(1-2):203-8.
298. Schoenberg MR, Mash KM, Bharucha KJ, Francel PC, Scott JG. Deep brain stimulation parameters associated with neuropsychological changes in subthalamic nucleus stimulation for refractory Parkinson's disease. *Stereotact Funct Neurosurg*. 2008;86(6):337-44.
299. Schreiber S, Shalev A. Lithium augmentation for mianserine-resistant depression in the elderly. [Hebrew]. *Harefuah*. 1992;123(7-8).
300. Schutter DJLG, Martin Laman D, Van Honk J, Vergouwen AC, Frank Koerselman G. Partial clinical response to 2 weeks of 2 Hz repetitive transcranial magnetic stimulation to the right parietal cortex in depression. *International Journal of Neuropsychopharmacology*. 2009 June;12(5):643-50.
301. Scott MA, Shelton PS, Gattis W. Therapeutic options for treating major depression, and the role of venlafaxine. *Pharmacotherapy*. 1996;16(3 I):352-65.
302. Seethalakshmi R, Krishnamoorthy ES. Depression in epilepsy: Phenomenology, diagnosis and management. *Epileptic Disorders*. 2007;9(1):1-10.
303. Segawa K, Azuma H, Sato K, Yasuda T, Arahata K, Otsuki K, et al. Regional cerebral blood flow changes in depression after electroconvulsive therapy. *Psychiatry Research Neuroimaging*. 2006;147(2-3):135-43.
304. Seifritz E, Hemmeter U, Poldinger W. Lithium-augmentation at therapy-resistant depressions. [German]. *TW Neurologie Psychiatrie*. 1994;8(4).
305. Serra M, Gasto C, Navarro V, Torres X, Blanch J, Masana G. Maintenance electroconvulsive therapy in elderly psychotic unipolar depression. *Medicina Clinica*. 2006;126(13):491-2.
306. Shabani A, Zolfigol F, Akbari M. Brief major depressive episode as an essential predictor of the Bipolar Spectrum Disorder. *Journal of Research in Medical Sciences*. 2009;14 (1):29-35.
307. Shapira B, Newman ME, Gelfin Y, Lerer B. Blunted temperature and cortisol responses to ipsapirone in major depression: lack of enhancement by electroconvulsive therapy. *Psychoneuroendocrinology*. 2000;25(5):421-38.
308. Shapira NA, Verduin ML, DeGraw JD. Treatment of refractory major depression with tramadol monotherapy [2] (multiple letters). *Journal of Clinical Psychiatry*. 2001;62 (3):205-6.
309. Sharma V. Loss of response to antidepressants and subsequent refractoriness: Diagnostic issues in a retrospective case series. *Journal of affective disorders*. 2001;64 (1):99-106.
310. Sharma V, Persad E. Pharmacotherapy of rapid cycling bipolar disorder: A review. *Lithium*. 1994;5(3):117-25.
311. Shrestha S, Shrestha BR, Thapa C, Pradhan SN, Thapa R, Adhikari S. Comparative study of esmolol and labetalol to attenuate haemodynamic responses after electroconvulsive therapy. *Kathmandu University Medical Journal*. 2007;5(19):318-23.
312. Shulman KI, Herrmann N. Bipolar disorder in old age. *Can Fam Physician*. 1999;45:1229-37.
313. Sicard D. Current aspects of AIDS. [French]. *Concours Medical*. 1990;112(29):2665-8.
314. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Ultra-brief pulse ECT in bipolar and unipolar depressive disorder: Differences in speed of response. *Bipolar Disorders*. 2009;11(4):418-24.
315. Simon NM, Kaufman RE, Hoge EA, Worthington JJ, Herlands NN, Owens ME, et al. Open-label support for duloxetine for the treatment of panic disorder. *CNS Neuroscience and Therapeutics*. 2009 Spring;15 (1):19-23.
316. Simuni T, Sethi K. Nonmotor manifestations of Parkinson's disease. *Annals of Neurology*. 2008;64(Suppl. 2):S65-S80.

317. Singleton AH, Rosenquist PB, Kimball J, McCall WV. Cardiac rhythm disturbance in a depressed patient after implantation with a vagus nerve stimulator. *Journal of ECT*. 2009 September;25(3):195-7.
318. Sluzewska A, Samborski W, Sobieska M, Klein R, Bosmans E, Rybakowski JK. Serotonin antibodies in relation to immune activation in major depression. *Human Psychopharmacology*. 1997;12(5):453-8.
319. Sobhan T, Sobhan FZ, Feldman JM, Ryan WG. Medication options for treatment-resistant schizophrenia: Implications for global mental health financing. *International Journal of Psychiatry in Clinical Practice*. 2006;10(3):213-9.
320. Soekadar SR, Arfeller C, Rilk A, Plontke SK, Plewnia C. Theta burst stimulation in the treatment of incapacitating tinnitus accompanied by severe depression. *CNS Spectrums*. 2009;14(4):208-11.
321. Sokolov STH, Joffe RT. Practical guidelines for combination drug therapy of treatment-resistant depression. *CNS Drugs*. 1995;4(5):341-50.
322. Sood N, Treglia M, Obenchain RL, Dulisse B, Melfi CA, Croghan TW. Determinants of antidepressant treatment outcome. *Am J Manag Care*. 2000;6(12):1327-36.
323. Sperling W, Reulbach U, Bleich S, Padberg F, Kornhuber J, Mueck-Weymann M. Cardiac effects of vagus nerve stimulation in patients with major depression. *Pharmacopsychiatry*. 2010;43(1):7-11.
324. Srinivasan SP, Hall JM, Leo RJ. Vocal cord dysfunction arising from vagal nerve stimulator removal. *American Journal of Psychiatry*. 2009 December;166(12):1412-3.
325. Starkstein SE, Migliorelli R. ECT in a patient with a frontal craniotomy and residual meningioma. *Journal of Neuropsychiatry and Clinical Neurosciences*. 1993;5(4):428-30.
326. Stek ML, van der Wurff FB, Uitdehaag BMJ, Beekman ATF, Hoogendijk WJG. ECT in the treatment of depressed elderly: lessons from a terminated clinical trial. *International Journal of Geriatric Psychiatry*. 2007;22(10):1052-4.
327. Stern WM, Tormos JM, Press DZ, Pearlman C, Pascual-Leone A. Antidepressant effects of high and low frequency repetitive transcranial magnetic stimulation to the dorsolateral prefrontal cortex: a double-blind, randomized, placebo-controlled trial. *J Neuropsychiatry Clin Neurosci*. 2007 Spring;19(2):179-86.
328. Strain SL. Fluoxetine-initiated ovulatory cycles in two clomiphene-resistant women [7]. *American Journal of Psychiatry*. 1994;151(4).
329. Stuart S, Wright JH, Thase ME, Beck AT. Cognitive therapy with inpatients. *General Hospital Psychiatry*. 1997;19(1):42-50.
330. Stuppach Ch H, De Col C, Honeder M, Kurz M, Meise U, Whitworth A. Treatment strategies in depression - An Austrian survey. [German]. *Neuropsychiatrie*. 1998;12(2):91-7.
331. Suslow T. Estimating verbal intelligence in unipolar depression: Comparison of word definition and word recognition. *Nordic Journal of Psychiatry*. 2009;63(2):120-3.
332. Suzuki M, Kimura M, Okazaki M, Hara K, Hino K, Watanabe M, et al. Spike-wave stupor during treatment with paroxetine: A case report. [Japanese]. *Journal of the Japan Epilepsy Society*. 2007;25(1):10-5.
333. Swann AC. Mixed or dysphoric manic states: psychopathology and treatment. *J Clin Psychiatry*. 1995;56(3 SUPPL.):6-10.
334. Swartz HA, Frank E. Psychotherapy for bipolar depression: a phase-specific treatment strategy? *Bipolar Disorders*. 2001;3(1):11-22.
335. Swiecicki L. Efficacy of citalopram in more than maximal dose in drug-resistant depression. Case report. [Polish]. *Psychiatria Polska*. 2003;37(5):839-44.
336. Tahir N. Serotonin syndrome as a consequence of drug-resistant infections: An interaction between linezolid and citalopram. *Journal of the American Medical Directors Association*. 2004;5(2):111-3.
337. Takechi K, Abe T, Yorozuya T, Watanabe T, Nagaro T. Refractory hypotension during general anaesthesia caused by the long-term use of amoxapine. *Anaesthesia and Intensive Care*. 2010 September;38 (5):965-6.

338. Taylor RS, Elston J. The use of surrogate outcomes in model-based cost-effectiveness analyses: a survey of UK Health Technology Assessment reports. *Health Technology Assessment*. 2009;13(8):iii-40.
339. Terry R. Vagus nerve stimulation: a proven therapy for treatment of epilepsy strives to improve efficacy and expand applications. Conference proceedings : . 2009;Annual International Conference of the IEEE Engineering in Medicine and Biology Society. IEEE Engineering in Medicine and Biology Society. Conference. 2009:4631-4.
340. Thase ME, Mallinger AG, McKnight D, Himmelhoch JM. Treatment of imipramine-resistant recurrent depression, IV: A double-blind crossover study of tranylcypromine for anergic bipolar depression. *American Journal of Psychiatry*. 1992;149(2):195-8.
341. Thompson C, Rodin I, Childs PA. Commentary on 'The management of treatment-resistant affective disorder: Clinical perspectives' [2]. *Journal of Psychopharmacology*. 1992;6(4):534-5.
342. Tolin DF, Frost RO, Steketee G. An open trial of cognitive-behavioral therapy for compulsive hoarding. *Behaviour Research and Therapy*. 2007;45(7):1461-70.
343. Tomruk NB, Saatcioglu O, Ugurlu E, Hacioglu M. ECT use in refractory obsessive-compulsive disorder. *Klinik Psikofarmakoloji Bulteni*. 2010;20 (2):167-70.
344. Tourigny-Rivard MF. Treatment of depression in the elderly. *Canadian Pharmaceutical Journal*. 1985;118 (6):286-7.
345. Tramontina JF, Andreatza AC, Kauer-Sant'Anna M, Stertz L, Goi J, Chiarani F, et al. Brain-derived neurotrophic factor serum levels before and after treatment for acute mania. *Neuroscience Letters*. 2009 13 Mar;452 (2):111-3.
346. Triezenberg D, Vachon D, Helmen J. How should you manage a depressed patient unresponsive to an SSRI? *Journal of Family Practice*. 2006;55(12):1081-2+7.
347. Tsiouris JA, Cohen IL, Patti PJ, Korosh WM. Treatment of previously undiagnosed psychiatric disorders in persons with developmental disabilities decreased or eliminated self-injurious behavior. *Journal of Clinical Psychiatry*. 2003 01 Sep;64 (9):1081-90.
348. Tundo A, Salvati L, Busto G, Di Spigno D, Falcini R. Addition of cognitive-behavioral therapy for nonresponders to medication for obsessive-compulsive disorder: A naturalistic study. *J Clin Psychiatry*. 2007;68(10):1552-6.
349. Ulzen TP, Powers RE. A review of empirical evidence of somatic treatment options for the MI/DD population. *Psychiatr Q*. 2008;79(3):265-73.
350. Ungvari GS, Leung Siu K, Wai-Kwong T, Ng Fung S. The pharmacological treatment of catatonia: An overview. *European Archives of Psychiatry and Clinical Neuroscience*. 2001;251(SUPPL. 1):31-4.
351. Unutzer J. Late-life depression. *New England Journal of Medicine*. 2007;357(22):2269-76.
352. Uzun O. Lamotrigine as an augmentation agent in treatment-resistant obsessive-compulsive disorder: A case report. *Journal of Psychopharmacology*. 2010 March;24 (3):425-7.
353. Uzun O, Ozdemir B. Aripiprazole as an augmentation agent in treatment-resistant body dysmorphic disorder. *Clinical Drug Investigation*. 2010;30 (10):707-10.
354. Van Den Brink G. The therapy of a depressive man. *Pharmacological reflections*. [Dutch]. *Pharmaceutisch Weekblad*. 1999;134(35):1212-8.
355. Van Den Broek WW, Groenland THN, Mulder PGH, Kusuma A, Birkenhager TK, Pluijms EM, et al. Beta-blockers and electroconvulsive therapy: a review. *Tijdschrift voor Psychiatrie*. 2008;50(4):205-12.
356. Van Der Starre PJA, Lemmens HJM, Chandel A, Solvason HB, Brock-Utne JG. The effects of esmolol and labetalol on cerebral blood flow velocity during electroconvulsive therapy [6]. *European Journal of Anaesthesiology*. 2008;25(2):174-6.

357. Van Praag HM. Treatment of refractory primary depression. [Dutch]. *Nederlands Tijdschrift voor Geneeskunde*. 1997;141(28):1375-9.
358. Van Zijl DH, Gordon PC, James MF. The comparative effects of remifentanyl or magnesium sulfate versus placebo on attenuating the hemodynamic responses after electroconvulsive therapy. *Anesth Analg*. 2005;101(6):1651-5.
359. Viikki M, Anttila S, Kampman O, Illi A, Huuhka M, Setälä-Soikkeli E, et al. Vascular endothelial growth factor (VEGF) polymorphism is associated with treatment resistant depression. *Neuroscience Letters*. 2010 June;477 (3):105-8.
360. Viikki M, Kampman O, Illi A, Setälä-Soikkeli E, Anttila S, Huuhka M, et al. TPH1 218A/C polymorphism is associated with major depressive disorder and its treatment response. *Neuroscience Letters*. 2010 01 Jan;468 (1):80-4.
361. Villeneuve A. Duration of treatment by antidepressants. [French]. *Encephale*. 1992;18(SPEC. ISS. IV):517-20.
362. Vinar O. Tianeptine helps depressed patients resistant to reuptake inhibitors and/or IMAO. *Homeostasis in Health and Disease*. 1999;39 (6):234-5.
363. Vishne T, Aronov S, Amiaz R, Etchin A, Grunhaus L. Remifentanyl supplementation of propofol during electroconvulsive therapy: effect on seizure duration and cardiovascular stability. *J ECT*. 2005;21(4):235-8.
364. Wajima Z, Shiga T, Imanaga K, Inoue T. Prophylactic continuous administration of landiolol, a novel beta1 blocker, blunts hyperdynamic responses during electroconvulsive therapy without altering seizure activity. *International Journal of Psychiatry in Clinical Practice*. 2010;14 (2):132-6.
365. Wajima Z, Yoshikawa T, Ogura A, Imanaga K, Shiga T, Inoue T, et al. The effects of diltiazem on hemodynamics and seizure duration during electroconvulsive therapy. *Anesth Analg*. 2001;92(5):1327-30.
366. Walder B, Seeck M, Tramer MR. Propofol versus methohexital for electroconvulsive therapy: a meta-analysis. *Journal of Neurosurgical Anesthesiology*. 2001;13(2):93-8.
367. Walker WR, Freeman RF, Christensen DK. Restricting Environmental Stimulation (REST) to enhance cognitive behavioral treatment for obsessive compulsive disorder with schizotypal personality disorder. *Behavior Therapy*. 1994;25(4):709-19.
368. Wang XM, Yang DB, Yu YF, Huang H, Zhao XQ. A controlled study of the treatment of repetitive transcranial magnetic stimulation in patients with major depression. *Chinese Journal of Clinical Rehabilitation* 2004:1770-1.
369. Wang YT, Yan F, Li ZQ, Du BG, Wang P, Zhang ZH. Effect of psychological intervention on in psychic anxiety family members of patients receiving modified electroconvulsive therapy. *Chinese Journal of Clinical Rehabilitation*. 2004;8(24):4956-7.
370. Warnell RL, Swartz CM, Thomson A. Propofol interruption of ECT seizure to reduce side-effects: A pilot study. *Psychiatry Research*. 2010 30 Jan;175(1-2):184-5.
371. Watson K, Summers KM. Depression in patients with heart failure: Clinical implications and management. *Pharmacotherapy*. 2009;29(1):49-63.
372. Weder ND, Muralee S, Penland H, Tampi RR. Catatonia: A review. *Annals of Clinical Psychiatry*. 2008;20(2):97-107.
373. Wehr TA. Manipulations of sleep and phototherapy: Nonpharmacological alternatives in the treatment of depression. *Clinical Neuropharmacology*. 1990;13(SUPPL. 1):S54-S65.
374. Weller EB, Weller RA. Treatment options in the management of adolescent depression. *Journal of Affective Disorders*. 2000;61(Suppl. 1):S23-S8.
375. Wells A, Welford M, Fraser J, King P, Mendel E, Wisely J, et al. Chronic PTSD treated with metacognitive therapy: an open trial. *Cognitive and Behavioral Practice*. 2008;15(1):85-92.

376. Wiethoff K, Bauer M, Baghai T, Heinz A, Adli M. Algorithms in the treatment of depression - The German Algorithm Project ("Berliner Algorithmusprojekt"). [German]. *Nervenheilkunde*. 2005;24(5):381-7.
377. Wilson K. Vascular disease, depression and cognitive impairment. *Encephale*. 2008;34(Suppl.2):S50-S4.
378. Wolkowitz OM. Rational polypharmacy in schizophrenia. *Annals of Clinical Psychiatry*. 1993;5(2):79-90.
379. Wong ICK, Tavernor SJ, Tavernor RME. Psychiatric adverse effects of anticonvulsant drugs: Incidence and therapeutic implications. *CNS Drugs*. 1997;8(6):492-509.
380. Wu CC, Tsai CH, Lu MK, Chen CM, Shen WC, Su KP. Theta-burst repetitive transcranial magnetic stimulation for treatment-resistant obsessive-compulsive disorder with concomitant depression. *Journal of Clinical Psychiatry*. 2010 April;71(4):504-6.
381. Wu L, Zou H, Zhou Q, Liu Z, Cheng B. Preemptive analgesia with butorphanol in psychotic patients following modified electroconvulsive therapy: A randomized controlled trial. *Neural Regeneration Research*. 2008;3(1):75-8.
382. Yamamoto S, Miyamoto T, Morita N, Yasuda M. Depressive disorders preceding temporal lobe epilepsy. *Epilepsy Research*. 2002;49 (2):153-6.
383. Yonkers KA, Wisner KL, Stowe Z, Leibenluft E, Cohen L, Miller L, et al. Management of bipolar disorder during pregnancy and the postpartum period. *Am J Psychiatry*. 2004;161(4):608-20.
384. Zacest A, Anderson VC, Burchiel KJ. The glass half empty or half full - How effective are long-term intrathecal opioids in post-herpetic neuralgia? a case series and review of the literature. *Neuromodulation*. 2009 July;12 (3):219-23.
385. Zarate Jr CA, Singh JB, Carlson PJ, Brutsche NE, Ameli R, Luckenbaugh DA, et al. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. *Arch Gen Psychiatry*. 2006;63(8):856-64.
386. Zarkowski P, Navarro R, Pavlicova M, George MS, Avery D. The effect of daily prefrontal repetitive transcranial magnetic stimulation over several weeks on resting motor threshold. *Brain Stimulation*. 2009 July;2(3):163-7.
387. Zhang Y, White PF, Thornton L, Perdue L, Downing M. The use of nicardipine for electroconvulsive therapy: a dose-ranging study. *Anesth Analg*. 2005 Feb;100(2):378-81.
388. Ziegler B. Antidepressant agents: Which drug is the best for the individual patient?. [German]. *Therapiewoche*. 1993;43(51-52):2752-5.
389. Zinetti J, Tenneze L, Rabus MT, Dare F. Addition of lithium carbonate and antidepressant drugs in resistant depression of elderly. [French]. *Revue de Geriatrie*. 1996;21(6).
390. Zvara DA, Brooker RF, McCall WV, Foreman AS, Hewitt C, Murphy BA, et al. The effect of esmolol on ST-segment depression and arrhythmias after electroconvulsive therapy. *Convuls Ther*. 1997 Sep;13(3):165-74.

**PsychInfo Database = 589 articles
(excluding duplicates)**

1. Mania Due to Ziprasidone Augmentation of a Selective Serotonin Reuptake Inhibitor. *Primary Psychiatry*. 2004 01;11(1):17-8.
2. Visual hallucinations due to the addition of riluzole to memantine and bupropion. *Primary Psychiatry*. 2006 06;13(6):25-6.
3. aan het Rot M, Collins KA, Murrough JW, Perez AM, Reich DL, Charney DS, et al. Safety and efficacy of repeated-dose intravenous ketamine for treatment-resistant depression. *Biological Psychiatry*. 2010;67(2):139-45.
4. Abarbanel JM, Lemberg T, Yaroslavski U, Grisaru N, et al. Electrophysiological responses to transcranial magnetic stimulation in depression and schizophrenia. *Biological Psychiatry*. 1996 Jul 1996;40(2):148-50.

5. Abraham G, Milev R, Lazowski L, Jokic R, du Toit R, Lowe A. Repetitive transcranial magnetic stimulation for treatment of elderly patients with depression--An open label trial. *Neuropsychiatric Disease and Treatment*. 2007;3(6):919-24.
6. Abramowitz MZ, Lichtenberg P, Marcus E-L, Shapira B. Treating a Holocaust survivor without addressing the Holocaust: a case report. *Clinical Gerontologist*. 1994;14(3):75-80.
7. Achiffer F, Stinchfield Z, Pascual-Leone A. Prediction of clinical response to transcranial magnetic stimulation for depression by baseline lateral visual-field stimulation. *Neuropsychiatry, Neuropsychology, & Behavioral Neurology*. 2002 Mar 2002;15(1):18-27.
8. Alonso-Navarro H, Jiménez-Jiménez FJ, Pilo-de-la-Fuente B, Plaza-Nieto JF. Panic attack-like episodes possibly associated with ropinirole. *Clinical neuropharmacology*. 2009;32(4):237-8.
9. Amiaz R, Stein O, Dannon PN, Grunhaus L, Schreiber S. Resolution of treatment-refractory depression with naltrexone augmentation of paroxetine: A case report. *Psychopharmacology*. 1999 Apr 1999;143(4):433-4.
10. Amsterdam JD. A 36-year-old man with a history of non-response to multiple medications: trials of various pharmacologic combinations may be necessary to find the correct treatment in some cases of resistant depression. *Psychiatric Annals*. 2004 Mar 2004;34(3):180-1.
11. Amsterdam JD, Chopra M. Monoamine oxidase inhibitors revisited. *Psychiatric Annals*. 2001;31(6):361-70.
12. Anderson B, Mishory A, Nahas Z, Borckardt JJ, Yamanaka K, Rastogi K, et al. Tolerability and safety of high daily doses of repetitive transcranial magnetic stimulation in healthy young men. *Journal of ECT*. 2006;22(1):49-53.
13. Anderson BS, Kavanagh K, Borckardt JJ, Nahas ZH, Kose S, Lisanby SH, et al. Decreasing procedural pain over time of left prefrontal rTMS for depression: Initial results from the open-label phase of a multisite trial (OPT-TMS). *Brain Stimulation*. 2009;2(2):88-92.
14. Anderson IM, Sarsfield A, Haddad PM. Efficacy, safety and tolerability of quetiapine augmentation in treatment resistant depression: An open-label, pilot study. *Journal of Affective Disorders*. 2009;117(1):116-9.
15. Antal A, Terney D, Kühnl S, Paulus W. Anodal transcranial direct current stimulation of the motor cortex ameliorates chronic pain and reduces short intracortical inhibition. *Journal of Pain and Symptom Management*. 2010;39(5):890-903.
16. Anwar N, Brakoulias V. Safety of electroconvulsive therapy after subdural haemorrhage. *Australian and New Zealand Journal of Psychiatry*. 2010;44(3).
17. Argyropoulos SV, Wheeler A, Nutt DJ. A case of reversal of treatment-resistant depression after almost 30 years of symptoms. *International Journal of Psychiatry in Clinical Practice*. 1999;12;3(4):289-91.
18. Arias L, O'Brien JJ, Kimball JN. Electroconvulsive therapy- and succinylcholine-related asystole. *The Journal of ECT*. 2009;25(2).
19. Arul-Anandam AP, Loo C, Martin D, Mitchell PB. Chronic neuropathic pain alleviation after transcranial direct current stimulation to the dorsolateral prefrontal cortex. *Brain Stimulation*. 2009;2(3):149-51.
20. Arul-Anandam AP, Loo C, Mitchell P. Induction of hypomanic episode with transcranial direct current stimulation. *The Journal of ECT*. 2010;26(1):68-9.
21. Ashton AK. A case report of high-dose transdermal selegiline in the treatment of major depressive disorder. *Annals of Clinical Psychiatry*. 2009;21(1):51-2.
22. Baeken C, Leyman L, De Raedt R, Vanderhasselt MA, D'Haenen H. Lack of impact of repetitive high frequency transcranial magnetic stimulation on mood in healthy female subjects. *Journal of Affective Disorders*. 2006 Jan 2006;90(1):63-6.

23. Baghai TC, di Michele F, Schüle C, Eser D, Zwanzger P, Pasini A, et al. Plasma concentrations of neuroactive steroids before and after electroconvulsive therapy in major depression. *Neuropsychopharmacology*. 2005 Jun 2005;30(6):1181-6.
24. Bajbouj M, Luborzewski A, Danker-Hopfe H, Lang UE. Motor cortical excitability in depressive patients after electroconvulsive therapy and repetitive transcranial magnetic stimulation. *Journal of ECT*. 2005 Dec 2005;21(4):243-5.
25. Bannan N. Multimodal therapy of treatment resistant depression: A study and analysis. *International Journal of Psychiatry in Medicine*. 2005 2005;35(1):27-39.
26. Bär K-J, Ebert A, Boettger MK, Merz S, Kiehltopf M, Jochum T, et al. Is successful electroconvulsive therapy related to stimulation of the vagal system? *Journal of Affective Disorders*. 2010;125(1-3):323-9.
27. Barak Y, Suholitsky H, Noy S. Moclobemide treatment of resistant depression in a patient with vascular dementia. *Human Psychopharmacology: Clinical and Experimental*. 1996 01;11(1):67-8.
28. Barbee JG, Conrad EJ, Jamhour NJ. Aripiprazole Augmentation in Treatment-Resistant Depression. *Annals of Clinical Psychiatry*. 2004 10;16(4):189-94.
29. Barbosa L, Berk M, Vorster M. A double-blind, randomized, placebo-controlled trial of augmentation with lamotrigine or placebo in patients concomitantly treated with fluoxetine for resistant major depressive episodes. *Journal of Clinical Psychiatry*. 2003 04;64(4):403-7.
30. Bares M, Brunovsky M, Kopecek M, Novak T, Stopkova P, Kozeny J, et al. Early reduction in prefrontal theta QEEG cordance value predicts response to venlafaxine treatment in patients with resistant depressive disorder. *European Psychiatry*. 2008 08;23(5):350-5.
31. Bares M, Kopecek M, Novak T, Stopkova P, Sos P, Kozeny J, et al. Low frequency (1-Hz), right prefrontal repetitive transcranial magnetic stimulation (rTMS) compared with venlafaxine ER in the treatment of resistant depression: A double-blind, single-centre, randomized study. *Journal of Affective Disorders*. 2009 11;118(1):94-100.
32. Bauer M, Bschor T, Kunz D, Berghöfer A, Ströhle A, Müller-Oerlinghausen B. Double-blind, placebo-controlled trial of the use of lithium to augment antidepressant medication in continuation treatment of unipolar major depression. *The American Journal of Psychiatry*. 2000 09;157(9):1429-35.
33. Bauer M, Hellweg R, Baumgartner A. Fluoxetine-induced akathisia does not reappear after switch to paroxetine. *Journal of Clinical Psychiatry*. 1996 12;57(12):593-4.
34. Baumann P, Broly F, Kosel M, Eap CB. Ultrarapid metabolism of clomipramine in a therapy-resistant depressive patient, as confirmed by CYP2 D6 genotyping. *Pharmacopsychiatry*. 1998 03;31(2):72-.
35. Bayless JD, McCormick LM, Brumm MC, Espe-Pfeifer PB, Long JJ, Lewis JL. Pre- and post-electroconvulsive therapy multidomain cognitive assessment in psychotic depression: Relationship to premorbid abilities and symptom improvement. *The Journal of ECT*. 2010;26(1):47-52.
36. Bech P, Olsen LRk, Jarløv N, Hammer M, Schütze T, Breum L. A case of sequential anti-stress medication in a patient with major depression resistant to amine-reuptake inhibitors. *Acta Psychiatrica Scandinavica*. 1999 07;100(1):76-8.
37. Beck S, Richardson SP, Shamim EA, Dang N, Schubert M, Hallett M. Short intracortical and surround inhibition are selectively reduced during movement initiation in focal hand dystonia. *Journal of Neuroscience*. 2008 Oct 2008;28(41):10363-9.
38. Bell C, Wilson S, Nutt DJ. Pindolol augmentation of sertraline in resistant depression and its effect on sleep. *Journal of Psychopharmacology*. 1998;12(1):105-7.

39. Bergmann TO, Mölle M, Marshall L, Kaya-Yildiz L, Born J, Roman Siebner H. A local signature of LTP- and LTD-like plasticity in human NREM sleep. *European Journal of Neuroscience*. 2008 May 2008;27(9):2241-9.
40. Bernardi S, Pallanti S. Successful duloxetine treatment of a binge eating disorder: A case report. *Journal of Psychopharmacology*. 2010;24(8):1269-72.
41. Bernik MrA, Corregiari FbM, Braun IMr. Panic attacks in the differential diagnosis and treatment of resistant epilepsy. *Depression and Anxiety*. 2002;15(4):190-2.
42. Bertschy G, Ragama-Pardos E, Aït-Ameur A, Muscionico M, Favre S, Roth L. Lithium augmentation in venlafaxine non-responders: An open study. *European Psychiatry*. 2003 10;18(6):314-7.
43. Bewernick BH, Hurlmann R, Matusch A, Kayser S, Grubert C, Hadrysiewicz B, et al. Nucleus accumbens deep brain stimulation decreases ratings of depression and anxiety in treatment-resistant depression. *Biological Psychiatry*. 2010;67(2):110-6.
44. Birkenhäger TK, van den Broek WW, Fekkes D, Mulder PG, Moleman P, Bruijn JA. Lithium addition in antidepressant-resistant depression: Effects on platelet 5-HT, plasma 5-HT and plasma 5-HIAA concentration. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2007 06;31(5):1084-8.
45. Birkenhäger TK, Pluijms EM, Ju MR, Mulder PG, van den Broek WW. Influence of age on the efficacy of electroconvulsive therapy in major depression: A retrospective study. *Journal of Affective Disorders*. 2010;126(1-2):257-61.
46. Birkenhäger TK, van den Broek WW, Wijkstra J, Bruijn JA, van Os E, Boks M, et al. Treatment of unipolar psychotic depression: An open study of lithium addition in refractory psychotic depression. *Journal of Clinical Psychopharmacology*. 2009;29(5):513-5.
47. Birmaher B, Waterman GS, Ryan ND, Perel J, McNabb J, Balach L, et al. Randomized, controlled trial of amitriptyline versus placebo for adolescents with 'treatment-resistant' major depression. *Journal of the American Academy of Child & Adolescent Psychiatry*. 1998 05;37(5):527-35.
48. Bishop J, Lane RC. Psychodynamic treatment of a case of grief superimposed on melancholia. *Clinical Case Studies*. 2003 Jan 2003;2(1):3-19.
49. Black W, Hoey P, Mayze T. Modafinil use in patients with a primary psychiatric illness. *Australian and New Zealand Journal of Psychiatry*. 2010;44(6):583-4.
50. Blazer DG. Late life affective disorders. *Archives of Gerontology and Geriatrics*. 1998 1998(6):43-7.
51. Bliem B, Müller-Dahlhaus JFM, Dinse HR, Ziemann U. Homeostatic metaplasticity in human somatosensory cortex. *Journal of Cognitive Neuroscience*. 2008 Aug 2008;20(8):1517-28.
52. Bloch Y, Grisaru N, Hard EV, Beitler G, Faivel N, Ratzoni G, et al. Repetitive transcranial magnetic stimulation in the treatment of depression in adolescents: An open-label study. *Journal of ECT*. 2008 Jun 2008;24(2):153-9.
53. Blumer D. Antidepressant and double antidepressant treatment for the affective disorder of epilepsy. *Journal of Clinical Psychiatry*. 1997 01;58(1):3-11.
54. Bodani M, Sheehan B, Philpot M. The use of dexamethasone in elderly patients with antidepressant-resistant depressive illness. *Journal of Psychopharmacology*. 1999;13(2):196-7.
55. Boggio PS, Berman F, Vergara AO, Muniz ALCR, Nahas FH, Leme PB, et al. Go-no-go task performance improvement after anodal transcranial DC stimulation of the left dorsolateral prefrontal cortex in major depression. *Journal of Affective Disorders*. 2007 Aug 2007;101(1):91-8.
56. Bonvicini C, Minelli A, Scassellati C, Bortolomasi M, Segala M, Sartori R, et al. Serotonin transporter gene polymorphisms and treatment-resistant depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010;34(6):934-9.

57. Bor J, Brunelin J, Rivet A, d'Amato T, Poulet E, Saoud M, et al. Effects of theta burst stimulation on glutamate levels in a patient with negative symptoms of schizophrenia. *Schizophrenia Research*. 2009;111(1-3):196-7.
58. Borckardt JJ, Anderson B, Kozel FA, Nahas Z, Smith AR, Thomas KJ, et al. Acute and long-term VNS effects on pain perception in a case of treatment-resistant depression. *Neurocase*. 2006 Aug 2006;12(4):216-20.
59. Borckardt JJ, Reeves ST, Weinstein M, Smith AR, Shelley N, Kozel FA, et al. Significant analgesic effects of one session of postoperative left prefrontal cortex repetitive transcranial magnetic stimulation: A replication study. *Brain Stimulation*. 2008 Apr 2008;1(2):122-7.
60. Borckardt JJ, Smith AR, Reeves ST, Weinstein M, Kozel FA, Nahas Z, et al. Fifteen minutes of left prefrontal repetitive transcranial magnetic stimulation acutely increases thermal pain thresholds in healthy adults. *Pain Research & Management*. 2007 Win 2007;12(4):287-90.
61. Borroni P, Montagna M, Cerri G, Baldissera F. Bilateral motor resonance evoked by observation of a one-hand movement: Role of the primary motor cortex. *European Journal of Neuroscience*. 2008 Oct 2008;28(7):1427-35.
62. Borson S, Raskind M. Antidepressant-resistant depression in the elderly. *Journal of the American Geriatrics Society*. 1986 Mar 1986;34(3):245-7.
63. Bottonari KA, Roberts JE, Thomas SN, Read JP. Stop thinking and start doing: switching from cognitive therapy to behavioral activation in a case of chronic treatment-resistant depression. *Cognitive and Behavioral Practice*. 2008 Nov 2008;15(4):376-86.
64. Boutros NN, Miano AP, Hoffman RE, Berman RM. EEG monitoring in depressed patients undergoing repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2001 Spr 2001;13(2):197-205.
65. Bowman ES, Coons PM. The use of electroconvulsive therapy in patients with dissociative disorders. *Journal of Nervous and Mental Disease*. 1992 Aug 1992;180(8):524-8.
66. Boylan LS, Flint LA, Labovitz DL, Jackson SC, Starner K, Devinsky O. Depression but not seizure frequency predicts quality of life in treatment-resistant epilepsy. *Neurology*. 2004 01;62(2):258-61.
67. Bramanti P, Grugno R, Vitetta A, Di Bella P, Muscará N, Nappi G. Migraine with and without aura: electrophysiological and functional neuroimaging evidence. *Functional Neurology*. 2005 Jan-Mar 2005;20(1):29-32.
68. Brambilla P, Perez J, Monchieri S, Rossini PM, Bonato C. Transient improvement of tardive dyskinesia induced with rTMS. *Neurology*. 2003 Oct 2003;61(8):1155.
69. Brent D, Emslie G, Clarke G, Wagner KD, Asarnow JR, Keller M, et al. Switching to another SSRI or to venlafaxine with or without cognitive behavioral therapy for adolescents with SSRI-resistant depression: The TORDIA randomized controlled trial. *Journal of the American Medical Association*. 2008 Feb 2008;299(8):901-13.
70. Brent DA, Emslie GJ, Clarke GN, Asarnow J, Spirito A, Ritz L, et al. Predictors of spontaneous and systematically assessed suicidal adverse events in the treatment of SSRI-resistant depression in adolescents (TORDIA) study. *The American Journal of Psychiatry*. 2009 04;166(4):418-26.
71. Brody AL, Saxena S, Fairbanks LA, Alborzian S, Demaree HA, Maidment KM, et al. Personality changes in adult subjects with major depressive disorder or obsessive-compulsive disorder treated with paroxetine. *Journal of Clinical Psychiatry*. 2000 05;61(5):349-55.
72. Brunelin J, Maklouf WB, Nicolas A, Saoud M, Poulet E. Successful switch to maintenance rTMS after maintenance ECT in refractory bipolar disorder. *Brain Stimulation*. 2010;3(4):238-9.

73. Brunoni AR, Teng CT, Correa C, Imamura M, Brasil-Neto JP, Boechat R, et al. Neuromodulation approaches for the treatment of major depression: Challenges and recommendations from a working group meeting. *Arquivos de Neuro-Psiquiatria*. 2010;68(3):433-51.
74. Busch AM, Uebelacker LA, Kalibatseva Z, Miller IW. Measuring homework completion in behavioral activation. *Behavior Modification*. 2010;34(4):310-29.
75. Callahan RJ. The impact of thought field therapy on heart rate variability. *Journal of Clinical Psychology*. 2001 Oct 2001;57(10):1153-70.
76. Cameron PM. Psychodynamic psychotherapy for the depressive syndrome. *Psychiatric Journal of the University of Ottawa*. 1989 Jun 1989;14(2):397-402.
77. Camprubi ME, Puri BK. The treatment of refractory depression using paroxetine with lithium augmentation. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 1995 05;19(3):515-7.
78. Carberry H. Psychological methods for helping the angry, resistant and negative patient. *Cognitive Rehabilitation*. 1983 Jul-Aug 1983;1(4):4-5.
79. Cardoso EF, Fregni F, Maia FM, Boggio PS, Myczkowski ML, Coracini K, et al. rTMS treatment for depression in Parkinson's disease increases BOLD responses in the left prefrontal cortex. *International Journal of Neuropsychopharmacology*. 2008 Mar 2008;11(2):173-83.
80. Carey JR, Evans CD, Anderson DC, Bhatt E, Nagpal A, Kimberley TJ, et al. Safety of 6-Hz primed low-frequency rTMS in stroke. *Neurorehabilitation & Neural Repair*. 2008 Mar-Apr 2008;22(2):185-92.
81. Carpenter LL, Milosavljevic N, Schechter JM, Tyrka AR, Price LH. Augmentation With Open-Label Atomoxetine for Partial or Nonresponse to Antidepressants. *Journal of Clinical Psychiatry*. 2005 10;66(10):1234-8.
82. Carpenter LL, Moreno FA, Kling MA, Anderson GM, Regenold WT, Labiner DM, et al. Effect of vagus nerve stimulation on cerebrospinal fluid monoamine metabolites, norepinephrine, and gamma-aminobutyric acid concentrations in depressed patients. *Biological Psychiatry*. 2004 Sep 2004;56(6):418-26.
83. Carty JA. An examination of the relative effectiveness of three cognitive behavioral group treatments for depression in an Australian treatment-resistant population. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2001 Jul 2001;62(1):539.
84. Carvalho AF, Nunes-Neto PR, Cavalcante JL, Lima MCO. Amisulpride augmentation after the failure of citalopram for depression: A case report. *Journal of Clinical Pharmacy and Therapeutics*. 2007 02;32(1):97-9.
85. Carvalho LA, Garner BA, Dew T, Fazakerley H, Pariante CM. Antidepressants, but not antipsychotics, modulate GR function in human whole blood: An insight into molecular mechanisms. *European Neuropsychopharmacology*. 2010;20(6):379-87.
86. Casamassima F, Lattanzi L, Perlis RH, Fratta S, Litta A, Longobardi A, et al. Efficacy of electroconvulsive therapy in Fahr disease associated with bipolar psychotic disorder: A Case Report. *The Journal of ECT*. 2009;25(3):213-5.
87. Cassano P, Lattanzi L, Fava M, Navari S, Battistini G, Abelli M, et al. Ropinirole in Treatment-Resistant Depression: A 16-Week Pilot Study. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*. 2005 05;50(6):357-60.
88. Cassano P, Lattanzi L, Soldani F, Navari S, Battistini G, Gemignani A, et al. Pramipexole in Treatment-Resistant Depression: An Extended Follow-Up. *Depression and Anxiety*. 2004;20(3):131-8.
89. Catafau AM, Perez V, Gironell A, Martin JC, Kulisevsky J, Estorch M, et al. SPECT mapping of cerebral activity changes induced by repetitive transcranial magnetic stimulation in depressed patients: A pilot study. *Psychiatry Res: Neuroimaging*. 2001 May 2001;106(3):151-60.

90. Cavanagh J, Patterson J, Pimlott S, Dewar D, Eersels J, Dempsey MF, et al. Serotonin Transporter Residual Availability During Long-Term Antidepressant Therapy Does Not Differentiate Responder and Nonresponder Unipolar Patients. *Biological Psychiatry*. 2006 02;59(4):301-8.
91. Chanpattana W, Kramer BA, Kunigiri G, Gangadhar BN, Kitphati R, Andrade C. A survey of the practice of electroconvulsive therapy in Asia. *The Journal of ECT*. 2010;26(1):5-10.
92. Chemtob CM, Novaco RW, Hamada RS, Gross DM. Cognitive-behavioral treatment for severe anger in posttraumatic stress disorder. *Journal of Consulting and Clinical Psychology*. 1997 Feb 1997;65(1):184-9.
93. Chouinard G, Steiner W. A case of mania induced by high-dose fluoxetine treatment. *The American Journal of Psychiatry*. 1986 05;143(5):686-.
94. Chung JPY, Yim PHW, Dunn ELW. Clinical and treatment characteristics of Chinese patients undergoing electroconvulsive therapy in an acute psychiatric unit in Hong Kong. *Hong Kong Journal of Psychiatry*. 2009;19(4):150-4.
95. Cohen D. Should the use of selective serotonin reuptake inhibitors in child and adolescent depression be banned? *Psychotherapy and Psychosomatics*. 2006 Dec 2006;76(1):5-14.
96. Cohen H, Kaplan Z, Kotler M, Kouperman I, Moisa R, Grisaru N. Repetitive transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in posttraumatic stress disorder: a double-blind, placebo-controlled study. *American Journal of Psychiatry*. 2004 Mar 2004;161(3):515-24.
97. Cohen MX, Axmacher N, Lenartz D, Elger CE, Sturm V, Schlaepfer TE. Nuclei accumbens phase synchrony predicts decision-making reversals following negative feedback. *The Journal of Neuroscience*. 2009;29(23):7591-8.
98. Conca A, Hrubos W, Di Pauli J, König P, Hausmann A. ECT response after relapse during continuation repetitive transcranial magnetic stimulation A case report. *European Psychiatry*. 2004 Apr 2004;19(2):118-9.
99. Conca A, König P, Hausmann A. Transcranial magnetic stimulation induces 'pseudoabsence seizure'. *Acta Psychiatrica Scandinavica*. 2000 Mar 2000;101(3):246-8.
100. Conca A, Peschina W, König P, Fritzsche H, Hausmann A. Effect of chronic repetitive transcranial magnetic stimulation on regional cerebral blood flow and regional cerebral glucose uptake in drug treatment-resistant depressives: A brief report. *Neuropsychobiology*. 2002 Jan 2002;45(1):27-31.
101. Conca A, Swoboda E, König P, Koppi S, Beraus W, Künz A, et al. Clinical impacts of single transcranial magnetic stimulation (sTMS) as an add-on therapy in severely depressed patients under SSRI treatment. *Hum Psychopharmacol: Clinical and Experimental*. 2000 Aug 2000;15(6):429-38.
102. Conus P, Bondolfi G, Eap CB, Macciardi F. Pharmacokinetic fluvoxamine-clomipramine interaction with favorable therapeutic consequences in therapy-resistant depressive patient. *Pharmacopsychiatry*. 1996 05;29(3):108-10.
103. Cooke RG, Levitan RD. Tryptophan for refractory bipolar spectrum disorder and sleep-phase delay. *Journal of Psychiatry & Neuroscience*. 2010;35(2).
104. Coric V, Taskiran S, Pittenger C, Wasylink S, Mathalon DH, Valentine G, et al. Riluzole Augmentation in Treatment-Resistant Obsessive-Compulsive Disorder: An Open-Label Trial. *Biological Psychiatry*. 2005 09;58(5):424-8.
105. Cornelius JR, Soloff PH, Perel JM, Ulrich RF. A preliminary trial of fluoxetine in refractory borderline patients. *Journal of Clinical Psychopharmacology*. 1991 04;11(2):116-20.
106. Crippa JAS, Hallak JEC, Zuardi AW, Chagas MHN, Quevedo J, Nardi AE. Agomelatine in the treatment of social anxiety disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010;34(7):1357-8.
107. Critchley HD, Lewis PA, Orth M, Josephs O, Deichmann R, Trimble MR, et al. Vagus nerve stimulation for treatment-resistant depression: behavioral and neural effects on encoding negative material. *Psychosomatic Medicine*. 2007 Jan 2007;69(1):17-22.

108. Cukiert A, Burattini JA, Cukiert CM, Argentoni-Baldochi M, Baise-Zung C, Forster CR, et al. Centro-median stimulation yields additional seizure frequency and attention improvement in patients previously submitted to callosotomy. *Seizure*. 2009;18(8):588-92.
109. Curtin F, Berney P, Kaufmann C. Moclobemide discontinuation syndrome predominantly presenting with influenza-like symptoms. *Journal of Psychopharmacology*. 2002 09;16(3):271-2.
110. Dannon PN, Grunhaus L. Effect of electroconvulsive therapy in repetitive transcranial magnetic stimulation non-responder MDD patients: A preliminary study. *International Journal of Neuropsychopharmacology*. 2001 Sep 2001;4(3):265-8.
111. Davanloo H. Intensive short-term dynamic psychotherapy: Technique of partial and major unlocking of the unconscious with a highly resistant patient: I Partial unlocking of the unconscious. *International Journal of Short-Term Psychotherapy*. 1995 Sep-Dec 1995;10(3):157-81.
112. Davenhill R, ed. Looking into later life: A psychoanalytic approach to depression and dementia in old age. London, England: Karnac Books 2007.
113. Davis A, Zisselman M, Simmons T, McCall WV, McCafferty J, Rosenquist PB. Electroconvulsive therapy in the setting of implantable cardioverter-defibrillators. *The Journal of ECT*. 2009;25(3):198-201.
114. Davis MH, Casey DA. Utilizing cognitive therapy on the short-term psychiatric inpatient unit. *General Hospital Psychiatry*. 1990 May 1990;12(3):170-6.
115. de la Fuente JR, Berlanga C, León-Andrade C. Mania induced by tricyclic-MAOI combination therapy in bipolar treatment-resistant disorder: Case reports. *Journal of Clinical Psychiatry*. 1986 01;47(1):40-1.
116. de Macedo-Soares MB, Moreno RA, Rigonatti SP, Lafer B. Efficacy of Electroconvulsive Therapy in Treatment-Resistant Bipolar Disorder: A Case Series. *The Journal of ECT*. 2005 03;21(1):31-4.
117. de Montigny C, Silverstone PH, Debonnel G, Blier P, Bakish D. Venlafaxine in treatment-resistant major depression: A Canadian multicenter, open-label trial. *Journal of Clinical Psychopharmacology*. 1999 10;19(5):401-6.
118. Dejonge P, Honig A, Van Melle JP, Schene AH, Kuyper AMG, Tulner D, et al. Nonresponse to treatment for depression following myocardial infarction: Association with subsequent cardiac events. *The American Journal of Psychiatry*. 2007 09;164(9):1371-8.
119. del Olmo MF, Bello O, Cudeiro J. Transcranial magnetic stimulation over dorsolateral prefrontal cortex in Parkinson's disease. *Clinical Neurophysiology*. 2007 Jan 2007;118(1):131-9.
120. Dell'Osso B, Dario A, Ciabatti M, Camuri G, Oldani L, Balossi I, et al. Vagus nerve stimulation in treatment-resistant bipolar depression. *Clinical Neuropsychiatry: Journal of Treatment Evaluation*. 2009;6(6):252-8.
121. Dell'Osso B, Mundo E, D'Urso N, Pozzoli S, Buoli M, Ciabatti MT, et al. Augmentative repetitive navigated transcranial magnetic stimulation (rTMS) in drug-resistant bipolar depression. *Bipolar Disorders*. 2009 Feb 2009;11(1):76-81.
122. Devarajan S, Ali J, Dursun SM. Quetiapine plus SSRI in treatment-resistant depression: Possible mechanisms. *Psychopharmacology*. 2006 04;185(3):402-3.
123. Devarajan S, Dursun SM. Olanzapine plus venlafaxine in treatment-resistant depression. *Journal of Psychopharmacology*. 2005 07;19(4):434-5.
124. Di Lazzaro V, Dileone M, Profice P, Pilato F, Oliviero A, Mazzone P, et al. LTD-like plasticity induced by paired associative stimulation: Direct evidence in humans. *Experimental Brain Research*. 2009 Apr 2009;194(4):661-4.
125. Dilbaz N, Sengü C, Okay T, Bayam Gk, Türkoglu A. The combined treatment of venlafaxine and ECT in treatment-resistant depressive patients. *International Journal of Psychiatry in Clinical Practice*. 2005 03;9(1):55-9.

126. Dinan T, Siggins L, Scully P, O'Brien S, Ross P, Stanton C. Investigating the inflammatory phenotype of major depression: Focus on cytokines and polyunsaturated fatty acids. *Journal of Psychiatric Research*. 2009 01;43(4):471-6.
127. Dolberg OT, Dannon PN, Schreiber S, Grunhaus L. Magnetic motor threshold and response to TMS in major depressive disorder. *Acta Psychiatrica Scandinavica*. 2002 Sep 2002;106(3):220-3.
128. Dolberg OT, Schreiber S, Grunhaus L. Transcranial magnetic stimulation-induced switch into mania: A report of two cases. *Biological Psychiatry*. 2001 Mar 2001;49(5):468-70.
129. Dudek D, Rybakowski JK, Siwek M, Pawłowski T, Lojko D, Roczeń R, et al. Risk factors of treatment resistance in major depression: Association with bipolarity. *Journal of Affective Disorders*. 2010;126(1-2):268-71.
130. Duhameau B, Ferré J-C, Jannin P, Gauvrit J-Y, Vérin M, Millet B, et al. Chronic and treatment-resistant depression: A study using arterial spin labeling perfusion MRI at 3 Tesla. *Psychiatry Research: Neuroimaging*. 2010;182(2):111-6.
131. Dunn NJ, Yanasak E, Schillaci J, Simotas S, Rehm LP, Soucek J, et al. Personality Disorders in Veterans With Posttraumatic Stress Disorder and Depression. *Journal of Traumatic Stress*. 2004 Feb 2004;17(1):75-82.
132. Ebert A, Jochum T, Ritter J, Boettger MK, Schulz S, Voss A, et al. Does parasympathetic modulation prior to ECT treatment influence therapeutic outcome? *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010;34(7):1174-80.
133. Egger C, Muehlbacher M, Grohmann R, Stuppaeck C. Clozapine intoxication in a patient with lamotrigine-induced rash. *Pharmacopsychiatry*. 2010;43(1):35-6.
134. Ehnvall A, Mitchell PB, Hadzi-Pavlovic D, Malhi GS, Parker G. Pain during depression and relationship to rejection sensitivity. *Acta Psychiatrica Scandinavica*. 2009;119(5):375-82.
135. Eisenberg J, Asnis G. Are antidepressant trials too short? A case report. *Journal of Clinical Psychiatry*. 1986 01;47(1):38-9.
136. Ella R, Zwanzger P, Stampfer R, Preuss UW, Müller-Siecheneder F, Möller H-J, et al. Switch to mania after slow rTMS of the right prefrontal cortex. *Journal of Clinical Psychiatry*. 2002 Mar 2002;63(3):249.
137. Elliott RE, Carlson C, Kalhorn SP, Moshel YA, Weiner HL, Devinsky O, et al. Refractory epilepsy in tuberous sclerosis: Vagus nerve stimulation with or without subsequent resective surgery. *Epilepsy & Behavior*. 2009;16(3):454-60.
138. Emsley RA, Buckley P, Jones AM, Greenwood MR. Differential effect of quetiapine on depressive symptoms in patients with partially responsive schizophrenia. *Journal of Psychopharmacology*. 2003 06;17(2):210-5.
139. Emslie GJ, Mayes T, Porta G, Vitiello B, Clarke G, Wagner KD, et al. Treatment of resistant depression in adolescents (TORDIA): Week 24 outcomes. *The American Journal of Psychiatry*. 2010;167(7):782-91.
140. Englisch S, Esser A, Zink M. Bupropion for depression in schizophrenia: A case report. *Pharmacopsychiatry*. 2010;43(1):38-9.
141. Epstein BH. The use of humor in cognitive-behavioral therapy with outpatient depressed male adolescents. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 1997 Mar 1997;57(9):5915.
142. Epstein CM, Figiel GS, McDonald WM, Amazon-Leece J, Figiel L. Rapid rate transcranial magnetic stimulation in young and middle-aged refractory depressed patients. *Psychiatric Annals*. 1998 Jan 1998;28(1):36-9.
143. Ergene E, Behr PK, Shih JJ. Quality-of-life assessment in patients treated with vagus nerve stimulation. *Epilepsy & Behavior*. 2001 Jun 2001;2(3):284-7.

144. Eschweiler GW, Plewnia C, Batra A, Bartels M. Does clinical response to repetitive prefrontal transcranial magnetic stimulation (rTMS) predict response to electroconvulsive therapy (ECT) in cases of major depression? *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*. 2000 Nov 2000;45(9):845-6.
145. Eschweiler GW, Wegerer C, Schlotter W, Spandl C, Stevens A, Bartels M, et al. Left prefrontal activation predicts therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychiatry Research: Neuroimaging*. 2000 Oct 2000;99(3):161-72.
146. Evers S, Hangst K, Pecuch PW. The impact of repetitive transcranial magnetic stimulation on pituitary hormone levels and cortisol in healthy subjects. *Journal of Affective Disorders*. 2001 Sep 2001;66(1):83-8.
147. Fagen TS, Wool CA. Conjoint therapy: Psychiatry and music therapy in the treatment of psychosomatic illness. *Int J Arts Medicine*. 1999 1999;6(1):4-9.
148. Fahy TJ. Side effects of moclobemide in depressed patients refractory to other treatments. *Irish Journal of Psychological Medicine*. 1993 Feb 1993;10(1):24-7.
149. Falconer DW, Cleland J, Fielding S, Reid IC. Using the Cambridge Neuropsychological Test Automated Battery (CANTAB) to assess the cognitive impact of electroconvulsive therapy on visual and visuospatial memory. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2010;40(6):1017-25.
150. Faravelli C, Albanesi G, Sessarego A. Viqualine in resistant depression: A double-blind, placebo-controlled trial. *Neuropsychobiology*. 1988;20(2):78-81.
151. Fasano A, Romito LM, Daniele A, Piano C, Zinno M, Bentivoglio AR, et al. Motor and cognitive outcome in patients with Parkinson's disease 8 years after subthalamic implants. *Brain: A Journal of Neurology*. 2010;133(9):2664-76.
152. Fava M, Alpert J, Nierenberg A, Lagomasino I, Sonawalla S, Tedlow J, et al. Double-blind study of high-dose fluoxetine versus lithium or desipramine augmentation of fluoxetine in partial responders and nonresponders to fluoxetine. *Journal of Clinical Psychopharmacology*. 2002 08;22(4):379-87.
153. Fawcett J. A 55-year-old Man With Long-term Refractory Depression. *Psychiatric Annals*. 2006 06;36(6):384-6.
154. Fàzzari G, Benzoni O, Sangaletti A, Bonera F, Nassini S, Mazzarini L, et al. Improvement of cognition in a patient with Cotard's delusions and frontotemporal atrophy receiving electroconvulsive therapy (ECT) for depression. *International Psychogeriatrics*. 2009;21(3):600-3.
155. Fe-Bornstein M, Watt SD, Gitlin MC. Improvement in the level of psychosocial functioning in chronic pain patients with the use of risperidone. *Pain Medicine*. 2002 06;3(2):128-31.
156. Fecteau GW. Treatment of posttraumatic stress reactions to traffic accidents. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2000 Jul 2000;61(1):527.
157. Feder R. Lithium augmentation of clomipramine. *Journal of Clinical Psychiatry*. 1988 11;49(11):458-.
158. Feijo de Mello M. Mirtazapine effectiveness in a patient with refractory psychotic depression. *International Journal of Psychiatry in Clinical Practice*. 1999 06;3(2):141-2.
159. Ferrucci R, Bortolomasi M, Vergari M, Tadini L, Salvoro B, Giacomuzzi M, et al. Transcranial direct current stimulation in severe, drug-resistant major depression. *Journal of Affective Disorders*. 2009 11;118(1):215-9.
160. Figiel GS, Epstein C, McDonald WM, Amazon-Leece J, Figiel L, Saldivia A, et al. The use of rapid-rate transcranial magnetic stimulation (rTMS) in refractory depressed patients. *Journal of Neuropsychiatry & Clinical Neurosciences*. 1998 Win 1998;10(1):20-5.

161. Fischer P, Tauscher J, Küfferle B, Kasper S. Weak antidepressant response after bupirone augmentation of serotonin reuptake inhibitors in refractory severe depression. *International Clinical Psychopharmacology*. 1998 03;13(2):83-6.
162. Fitzgerald PB, Benitez J, de Castella AR, Brown TL, Daskalakis ZJ, Kulkarni J. Naturalistic study of the use of transcranial magnetic stimulation in the treatment of depressive relapse. *Australian and New Zealand Journal of Psychiatry*. 2006 Sep 2006;40(9):764-8.
163. Fitzgerald PB, Hoy K, Daskalakis ZJ, Kulkarni J. A randomized trial of the antidepressant effects of low- and high-frequency transcranial magnetic stimulation in treatment-resistant depression. *Depression and Anxiety*. 2009 Mar 2009;26(3):229-34.
164. Fontaine D, Lanteri-Minet M, Ouchchane L, Lazorthes Y, Mertens P, Blond S, et al. Anatomical location of effective deep brain stimulation electrodes in chronic cluster headache. *Brain: A Journal of Neurology*. 2010;133(4):1214-23.
165. Fontaine D, Lazorthes Y, Mertens P, Blond S, Géraud G, Fabre N, et al. Safety and efficacy of deep brain stimulation in refractory cluster headache: A randomized placebo-controlled double-blind trial followed by a 1-year open extension. *The Journal of Headache and Pain*. 2010;11(1):23-31.
166. Ford HE, Jenike MA. Erythema multiforme associated with trazodone therapy: Case report. *Journal of Clinical Psychiatry*. 1985 07;46(7):294-5.
167. Fostick L, Silberman A, Beckman M, Spivak B, Amital D. The economic impact of depression: Resistance or severity? *European Neuropsychopharmacology*. 2010;20(10):671-5.
168. Frank E, Grochocinski VJ, Spanier CA, Buysse DJ, Cherry CR, Houck PR, et al. Interpersonal psychotherapy and antidepressant medication: Evaluation of a sequential treatment strategy in women with recurrent major depression. *Journal of Clinical Psychiatry*. 2000 Jan 2000;61(1):51-7.
169. Franzini A, Messina G, Gambini O, Muffatti R, Scarone S, Cordella R, et al. Deep-brain stimulation of the nucleus accumbens in obsessive compulsive disorder: Clinical, surgical and electrophysiological considerations in two consecutive patients. *Neurological Sciences*. 2010;31(3):353-9.
170. Fregni F, Merabet L, Pascual-Leone A, Marcolin MA. Modulation in motor threshold after a severe episode of gastrointestinal distress. *Journal of ECT*. 2004 2004;20(1):50-1.
171. Fujita K, Koga Y. Clinical application of single-pulse transcranial magnetic stimulation for the treatment of depression. *Psychiatry and Clinical Neurosciences*. 2005 Aug 2005;59(4):425-32.
172. Furubayashi T, Terao Y, Arai N, Okabe S, Mochizuki H, Hanajima R, et al. Short and long duration transcranial direct current stimulation (tDCS) over the human hand motor area. *Experimental Brain Research*. 2008 Feb 2008;185(2):279-86.
173. Fux M, Benjamin J, Nemets B. A placebo-controlled cross-over trial of adjunctive EPA in OCD. *Journal of Psychiatric Research*. 2004 05;38(3):323-5.
174. Garber A, Gregory RJ. Benzotropine in the treatment of venlafaxine-induced sweating. *Journal of Clinical Psychiatry*. 1997 Apr 1997;58(4):176-7.
175. Garcia RF, Dias AG, de Freitas AR, Fontenelle LF. Short-lived response of cervical dystonia to electroconvulsive therapy. *The Journal of ECT*. 2009;25(2):135-6.
176. Garcia-Toro M, Pascual-Leone A, Romera M, Gonzalez A, Micó J, Ibarra O, et al. Prefrontal repetitive transcranial magnetic stimulation as add on treatment for depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2001 Oct 2001;71(4):546-8.
177. Garety PA, Kuipers L, Fowler D, Chamberlain F, et al. Cognitive behavioural therapy for drug-resistant psychosis. *British Journal of Medical Psychology*. 1994 Sep 1994;67(3):259-71.

178. Gazdag G, Molnár E, Ungvari GS, Iványi Z. Knowledge of and attitude toward electroconvulsive therapy: A survey of Hungarian anesthesiology residents. *The Journal of ECT*. 2009;25(2):113-6.
179. Geller V, Grisaru N, Abarbanel JM, Lemberg T, Belmaker RH. Slow magnetic stimulation of prefrontal cortex in depression and schizophrenia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 1997 Jan 1997;21(1):105-10.
180. George MS, Nahas Z, Molloy M, Speer AM, Oliver NC, Li X-B, et al. A controlled trial of daily left prefrontal cortex TMS for treating depression. *Biological Psychiatry*. 2000 Nov 2000;48(10):962-70.
181. George MS, Sackeim HA, Marangell LB, Husain MM, Nahas Z, Lisanby SH, et al. Vagus nerve stimulation: A potential therapy for resistant depression? *Psychiatric Clinics of North America*. 2000 Dec 2000;23(4):757-83.
182. George MS, Speer AM, Molloy M, Nahas Z, Teneback CC, Risch SC, et al. Low frequency daily left prefrontal rTMS improves mood in bipolar depression: A placebo-controlled case report. *Human Psychopharmacology: Clinical and Experimental*. 1998 Jun 1998;13(4):271-5.
183. George MS, Ward HE, Jr., Ninan PT, Pollack M, Nahas Z, Anderson B, et al. A pilot study of vagus nerve stimulation (VNS) for treatment-resistant anxiety disorders. *Brain Stimulation*. 2008 Apr 2008;1(2):112-21.
184. George MS, Wassermann EM, Williams WA, Callahan A, et al. Daily repetitive transcranial magnetic stimulation (rTMS) improves mood in depression. *Neuroreport: An International Journal for the Rapid Communication of Research in Neuroscience*. 1995 Oct 1995;6(14):1853-6.
185. George T, Theodoros MT, Chiu E, Krapivensky N, Hokin A, Tiller JWG. An open study of sertraline in patients with major depression who failed to respond to moclobemide. *Australian and New Zealand Journal of Psychiatry*. 1999 12;33(6):889-95.
186. Germain A, Shear MK, Hall M, Buysse DJ. Effects of a brief behavioral treatment for PTSD-related sleep disturbances: A pilot study. *Behaviour Research and Therapy*. 2007 Mar 2007;45(3):627-32.
187. Ginsberg DL. Adjunctive Ropinirole for Treatment-Resistant Depression. *Primary Psychiatry*. 2005 08;12(8):26-7.
188. Ginsberg DL. Aripiprazole Augmentation for Treatment-Resistant Depression. *Primary Psychiatry*. 2005 06;12(6):26-7.
189. Ginsberg DL. Transdermal (but not oral) selegiline effective for treatment-resistant depression. *Primary Psychiatry*. 2007;14(7).
190. Glezer A, Murray E, Price B, Cunningham M. Effective use of electroconvulsive therapy after craniofacial reconstructive surgery. *The Journal of ECT*. 2009;25(3):208-9.
191. Goldberg JF, Burdick KE, Endick CJ. Preliminary Randomized, Double-Blind, Placebo-Controlled Trial of Pramipexole Added to Mood Stabilizers for Treatment-Resistant Bipolar Depression. *The American Journal of Psychiatry*. 2004 03;161(3):564-6.
192. Goldstein BI, Shamseddeen W, Spirito A, Emslie G, Clarke G, Wagner KD, et al. Substance use and the treatment of resistant depression in adolescents. *Journal of the American Academy of Child & Adolescent Psychiatry*. 2009;48(12):1182-92.
193. Gonul AS, Akdeniz F, Donat O, Vahip S. Selective serotonin reuptake inhibitors combined with venlafaxine in depressed patients who had partial response to venlafaxine: Four cases. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2003 08;27(5):889-91.
194. Goodman WK, Foote KD, Greenberg BD, Ricciuti N, Bauer R, Ward H, et al. Deep brain stimulation for intractable obsessive compulsive disorder: Pilot study using a blinded, staggered-onset design. *Biological Psychiatry*. 2010;67(6):535-42.
195. Gormly N, Cullen C, Watters L, Philpot M, Lawlor BA. Does psychosis predict response to ECT in depressed elderly patients? *Irish Journal of Psychological Medicine*. 1999 Mar 1999;16(1):13-5.

196. Govender S, Drummond LM, Menzies RG. Danger ideation reduction therapy for the treatment of severe, chronic and resistant obsessive-compulsive disorder. *Behavioural and Cognitive Psychotherapy*. 2006 Oct 2006;34(4):477-80.
197. Graf T, Engeler J, Achermann P, Mosimann UP, Noss R, Fisch H-U, et al. High frequency repetitive transcranial magnetic stimulation (rTMS) of the left dorsolateral cortex: EEG topography during waking and subsequent sleep. *Psychiatry Research: Neuroimaging*. 2001 Jul 2001;107(1):1-9.
198. Graff-Radford J, Foote KD, Mikos AE, Bowers D, Fernandez HH, Rosado CA, et al. Mood and motor effects of thalamic deep brain stimulation surgery for essential tremor. *European Journal of Neurology*. 2010;17(8):1040-6.
199. Greenberg BD, Gabriels LA, Malone DA, Jr., Rezai AR, Friehs GM, Okun MS, et al. Deep brain stimulation of the ventral internal capsule/ventral striatum for obsessive-compulsive disorder: Worldwide experience. *Molecular Psychiatry*. 2010;15(1):64-79.
200. Grimm S, Beck J, Schuepbach D, Hell D, Boesiger P, Birmphol F, et al. Imbalance between left and right dorsolateral prefrontal cortex in major depression is linked to negative emotional judgment: An fMRI study in severe major depressive disorder. *Biological Psychiatry*. 2008 Feb 2008;63(4):369-76.
201. Grisar N, Bruno R, Pridmore S. Effect on the emotions of healthy individuals of slow repetitive transcranial magnetic stimulation applied to the prefrontal cortex. *Journal of ECT*. 2001 Sep 2001;17(3):184-9.
202. Grunhaus L, Dolberg OT, Polak D, Dannon PN. Monitoring the response to rTMS in depression with visual analog scales. *Human Psychopharmacology: Clinical and Experimental*. 2002 Oct 2002;17(7):349-52.
203. Guinjoan SM, Mayberg HS, Costanzo EY, Fahrner RD, Tenca E, Antico J, et al. Asymmetrical contribution of brain structures to treatment-resistant depression as illustrated by effects of right subgenual cingulum stimulation. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2010;22(3):265-77.
204. Habel U, Wild B, Topka H, Kircher T, Salloum JB, Schenider F. Transcranial magnetic stimulation: No effect on mood with single pulse during learned helplessness. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2001 Apr 2001;25(3):497-506.
205. Hamner MB, Frueh BC. Response to venlafaxine in a previously antidepressant treatment-resistant combat veteran with post-traumatic stress disorder. *International Clinical Psychopharmacology*. 1998 09;13(5):233-4.
206. Harden CL, Pulver MC, Ravdin LD, Nikolov B, Halper JP, Labar DR. A pilot study of mood in epilepsy patients treated with vagus nerve stimulation. *Epilepsy & Behavior*. 2000 Apr 2000;1(2):93-9.
207. Hausmann A, Mangweth B, Walpöth M, Hoertnagel C, Kramer-Reinstadler K, Rupp CI, et al. Repetitive transcranial magnetic stimulation (rTMS) in the double-blind treatment of a depressed patient suffering from bulimia nervosa: A case report. *International Journal of Neuropsychopharmacology*. 2004 Sep 2004;7(3):371-3.
208. Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, et al. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *Journal of Clinical Psychiatry*. 2004 Jun 2004;65(6):772-82.
209. Hawley C, Sivakumaran T, Huber TJ, Ige AK. Combination therapy with nefazodone and lithium: Safety and tolerability in fourteen patients. *International Journal of Psychiatry in Clinical Practice*. 1998 12;2(4):251-4.
210. He W, Chai H, Zheng L, Yu W, Chen W, Li J, et al. Mismatch negativity in treatment-resistant depression and borderline personality disorder. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010;34(2):366-71.
211. Hellerstein DJ, Batchelder S, Hyler S, Arnaout B, Corpuz V, Coram L, et al. Aripiprazole as an adjunctive treatment for refractory unipolar depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2008 04;32(3):744-50.

212. Hennings JM, Owashi T, Binder EB, Horstmann S, Menke A, Kloiber S, et al. Clinical characteristics and treatment outcome in a representative sample of depressed inpatients--Findings from the Munich Antidepressant Response Signature (MARS) project. *Journal of Psychiatric Research*. 2009 01;43(3):215-29.
213. Herwig U, Bräuer K, Connemann B, Spitzer M, Schönfeldt-Lecuona C. Intracortical excitability is modulated by a norepinephrine-reuptake inhibitor as measured with paired-pulse transcranial magnetic stimulation. *Psychopharmacology*. 2002 Nov 2002;164(2):228-32.
214. Herwig U, Lampe Y, Juengling FD, Wunderlich A, Walter H, Spitzer M, et al. Add-on rTMS for treatment of depression: a pilot study using stereotaxic coil-navigation according to PET data. *Journal of Psychiatric Research*. 2003 Jul-Aug 2003;37(4):267-75.
215. Higuchi H, Kamata M, Sugawara Y, Yoshida K. Remarkable Effect of Selegiline (L-Deprenyl), a Selective Monoamine Oxidase Type-B Inhibitor, in a Patient With Severe Refractory Depression: A Case Report. *Clinical Neuropharmacology*. 2005 07;28(4):191-2.
216. Hirschmann S, Dannon PN, Iancu I, Dolberg OT, Zohar J, Grunhaus L. Pindolol augmentation in patients with treatment-resistant panic disorder: A double-blind, placebo controlled trial. *Journal of Clinical Psychopharmacology*. 2000 10;20(5):556-9.
217. Höflich G, Kasper S, Hufnagel A, Ruhrmann S, Möller H-J. Application of transcranial magnetic stimulation in treatment of drug-resistant major depression: A report of two cases. *Human Psychopharmacology: Clinical and Experimental*. 1993 Sep-Oct 1993;8(5):361-5.
218. Holroyd S, Durgee J. Venlafaxine in treatment refractory geriatric depression. *Clinical Gerontologist: The Journal of Aging and Mental Health*. 1998;18(3):39-50.
219. Holtzheimer P, Fawaz W, Wilson C, Avery D. Repetitive transcranial magnetic stimulation may induce language switching in bilingual patients. *Brain and Language*. 2005 Sep 2005;94(3):274-7.
220. Hoppe C, Helmstaedter C, Scherrmann J, Elger CE. Self-reported mood changes following 6 months of vagus nerve stimulation in epilepsy patients. *Epilepsy & Behavior*. 2001 Aug 2001;2(4):335-42.
221. Höppner J, Schulz M, Irmisch G, Mau R, Schläfke D, Richter J. Antidepressant efficacy of two different rTMS procedures: High frequency over left versus low frequency over right prefrontal cortex compared with sham stimulation. *European Archives of Psychiatry and Clinical Neuroscience*. 2003 2003;253(2):103-9.
222. Hoy KE, Fitzgerald PB. Introducing magnetic seizure therapy: A novel therapy for treatment resistant depression. *Australian and New Zealand Journal of Psychiatry*. 2010;44(7):591-8.
223. Hrdlicka M. Combination of clozapine and maprotiline in refractory psychotic depression. *European Psychiatry*. 2002 12;17(8):484-.
224. Hsueh K-L, Lin P-Y. Treatment-resistant depression prior to the diagnosis of cryptococcal meningitis: A case report. *General Hospital Psychiatry*. 2010;32(5):e9-e10.
225. Hu Y, Yu X, Yang F, Si T, Wang W, Tan Y, et al. The level of serum brain-derived neurotrophic factor is associated with the therapeutic efficacy of modified electroconvulsive therapy in Chinese patients with depression. *The Journal of ECT*. 2010;26(2):121-5.
226. Huang Y-Z, Rothwell JC, Edwards MJ, Chen R-S. Effect of physiological activity on an NMDA-dependent form of cortical plasticity in human. *Cerebral Cortex*. 2008 Mar 2008;18(3):563-70.
227. Huber R, Määttä S, Esser SK, Sarasso S, Ferrarelli F, Watson A, et al. Measures of cortical plasticity after transcranial paired associative stimulation predict changes in electroencephalogram slow-wave activity during subsequent sleep. *Journal of Neuroscience*. 2008 Jul 2008;28(31):7911-8.
228. Husain MM, Stegman D, Trevino K. Pregnancy and delivery while receiving vagus nerve stimulation for the treatment of major depression: A case report. *Annals of General Psychiatry*. 2005 Sept 2005;4:ArtID 16.

229. Hustig H, Onilov R. ECT rekindles pharmacological response in schizophrenia. *European Psychiatry*. 2009;24(8):521-5.
230. Iosifescu DV, Clementi-Craven N, Fraguas R, Papakostas GI, Petersen T, Alpert JE, et al. Cardiovascular Risk Factors May Moderate Pharmacological Treatment Effects in Major Depressive Disorder. *Psychosomatic Medicine*. 2005 09;67(5):703-6.
231. Iosifescu DV, Nierenberg AA, Mischoulon D, Perlis RH, Papakostas GI, Ryan JL, et al. An Open Study of Triiodothyronine Augmentation of Selective Serotonin Reuptake Inhibitors in Treatment-Resistant Major Depressive Disorder. *Journal of Clinical Psychiatry*. 2005 08;66(8):1038-42.
232. Isenberg K, Downs D, Pierce K, Svarakic D, Garcia K, Jarvis M, et al. Low Frequency rTMS Stimulation of the Right Frontal Cortex Is as Effective as High Frequency rTMS Stimulation of the Left Frontal Cortex for Antidepressant-Free, Treatment-Resistant Depressed Patients. *Annals of Clinical Psychiatry*. 2005 Jul-Sep 2005;17(3):153-9.
233. Israël M, Steiger H, Koliakakis T, McGregor L, Sadikot AF. Deep brain stimulation in the subgenual cingulate cortex for an intractable eating disorder. *Biological Psychiatry*. 2010;67(9):e53-e4.
234. Ivanova JI, Birnbaum HG, Kidolezi Y, Subramanian G, Khan SA, Stensland MD. Direct and indirect costs of employees with treatment-resistant and non-treatment-resistant major depressive disorder. *Current Medical Research and Opinion*. 2010;26(10):2475-84.
235. Iwata K, Masuda M, Soejima K, Ohashi M. Combination of electroconvulsive therapy with skin graft surgery for a schizophrenic patient with burns. *The Journal of ECT*. 2009;25(3):210-2.
236. Jaafari N, Brzozowski M, Rotge JY, Sharov I, Bates H, Paillot C, et al. ECT as a 'therapeutic test' to differentiate pharmacoresistant depression from dementia in the elderly: A pilot study. *Primary Care & Community Psychiatry*. 2008;13(4):155-61.
237. Janssen J, Pol HEH, Schnack HG, Kok RM, Lampe IK, de Leeuw F-E, et al. Cerebral volume measurements and subcortical white matter lesions and short-term treatment response in late life depression. *International Journal of Geriatric Psychiatry*. 2007 05;22(5):468-74.
238. Jeyapaul P, Vieweg R. A case study evaluating the use of clozapine in depression with psychotic features. *Annals of General Psychiatry*. 2006 11;5.
239. Joffe H, Groninger H, Soares C, Nonacs R, Cohen LS. An open trial of mirtazapine in menopausal women with depression unresponsive to estrogen replacement therapy. *Journal of Women's Health & Gender-Based Medicine*. 2001 12;10(10):999-1004.
240. Johnson BA, Cowen PJ. Calcium channel blockade and resistant bipolar depression. *Irish Journal of Psychological Medicine*. 1991 Mar 1991;8(1):50-1.
241. Juruena MF, Pariante CM, Papadopoulos As, Poon L, Lightman S, Cleare AJ. Prednisolone suppression test in depression: Prospective study of the role of HPA axis dysfunction in treatment resistance. *British Journal of Psychiatry*. 2009 04;194(4):342-9.
242. Kalayam B, Alexopoulos GS. Prefrontal dysfunction and treatment response in geriatric depression. *Archives of General Psychiatry*. 1999 08;56(8):713-8.
243. Kamath V, Kamath S, Ramkissoon R. Maintenance ECT over nine years in schizoaffective disorder. *German Journal of Psychiatry*. 2010;13(2):100-3.
244. Kanai A, Okamoto H. Paroxetine improves pain and depression in patients with refractory chronic pain. *The Pain Clinic*. 2007;19(5):235-9.
245. Kaplan EM. Efficacy of venlafaxine in patients with major depressive disorder who have unsustained or no response to selective serotonin reuptake inhibitors: An open-label, uncontrolled study. *Clinical Therapeutics: The International Peer-Reviewed Journal of Drug Therapy*. 2002 07;24(7):1194-200.

246. Kapstan A, Yaroslavsky Y, Applebaum J, Belmaker RH, Grisaru N. Right prefrontal TMS versus sham treatment of mania: A controlled study. *Bipolar Disorders*. 2003 Feb 2003;5(1):36-9.
247. Karp JF, Reynolds CF, III. Pharmacotherapy of Depression in the Elderly: Achieving and Maintaining Optimal Outcomes. *Primary Psychiatry*. 2004 May 2004;11(5):37-46.
248. Katona CLE, Abou-Saleh MT, Harrison DA, Nairac BA. Placebo-controlled trial of lithium augmentation of fluoxetine and lofepramine. *British Journal of Psychiatry*. 1995 01;166:80-6.
249. Katsikitis M, Pridmore S, Marzullo M. The facial expression measurement system in the assessment of the efficacy of transcranial magnetic stimulation in the treatment of depression. *European Review of Applied Psychology*. 1999 1999;49(2):123-9.
250. Kaya B, Güzelipek M, Özcan ME. Severe extrapyramidal symptoms due to sulpiride and fluoxetine combination in a case of OCD. *Klinik Psikofarmakoloji Bülteni*. 2001;11(2):121-3.
251. Kayser S, Bewernick B, Axmacher N, Schlaepfer TE. Magnetic seizure therapy of treatment-resistant depression in a patient with bipolar disorder. *The Journal of ECT*. 2009 06;25(2):137-40.
252. Keddy P, Erdberg P. Changes in the Rorschach and MMPI-2 after electroconvulsive therapy (ECT): A collaborative assessment case study. *Journal of Personality Assessment*. 2010;92(4):279-95.
253. Keitner GI, Garlow SJ, Ryan CE, Ninan PT, Solomon DA, Nemeroff CB, et al. A randomized, placebo-controlled trial of risperidone augmentation for patients with difficult-to-treat unipolar, non-psychotic major depression. *Journal of Psychiatric Research*. Netherlands: Elsevier Science 2009:205-14.
254. Kellner CH, Tobias KG, Jakubowski LM, Ali Z, Istafanous RM. Electroconvulsive therapy for an urgent social indication. *The Journal of ECT*. 2009;25(4):274-5.
255. Kellner M. Aripiprazole in a therapy-resistant patient with borderline personality and post-traumatic stress disorder. *Pharmacopsychiatry*. 2007 Jan 2007;40(1):41.
256. Kelly T, Lieberman DZ. The use of triiodothyronine as an augmentation agent in treatment-resistant bipolar II and bipolar disorder NOS. *Journal of Affective Disorders*. 2009;116(3):202-26.
257. Kemp DE, Gilmer WS, Fleck J, Straus JL, Dago PL, Karaffa M. Aripiprazole augmentation in treatment-resistant bipolar depression: Early response and development of akathisia. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2007 03;31(2):574-7.
258. Kemp DE, Ismail-Beigi F, Calabrese JR. Antidepressant response associated with pioglitazone: Support for an overlapping pathophysiology between major depression and metabolic syndrome. *The American Journal of Psychiatry*. 2009;166(5).
259. Kennard BD, Clarke GN, Weersing VR, Asarnow JR, Shamseddeen W, Porta G, et al. Effective components of TORDIA cognitive-behavioral therapy for adolescent depression: Preliminary findings. *Journal of Consulting and Clinical Psychology*. 2009;77(6):1033-41.
260. Kennedy SH, Segal ZV, Cohen NL, Levitan RD, Gemar M, Bagby RM. Lithium carbonate versus cognitive therapy as sequential combination treatment strategies in partial responders to antidepressant medication: An exploratory trial. *Journal of Clinical Psychiatry*. 2003 Apr 2003;64(4):439-44.
261. Kennedy T, Jones R, Darnley S, Seed P, Wessely S, Chalder T. Cognitive behaviour therapy in addition to antispasmodic treatment for irritable bowel syndrome in primary care: Randomised controlled trial. *British Medical Journal*. 2005 Aug 2005;331(7514):435.
262. Kenny MA, Williams JMG. Treatment-resistant depressed patients show a good response to Mindfulness-based Cognitive Therapy. *Behaviour Research and Therapy*. 2007 Mar 2007;45(3):617-25.

263. Kent LK, Weston CA, Heyer EJ, Sherman W, Prudic J. Successful retrieval of ECT two months after ECT-induced takotsubo cardiomyopathy. *The American Journal of Psychiatry*. 2009;166(8):857-62.
264. Khan AY, Golewale M. Significant weight loss in a young adult man. *Psychiatric Annals*. 2007 Mar 2007;37(3):152, 4-7.
265. Kibler JL, Lyons JA. Brief cognition-focused group therapy for depressive symptoms in chronic posttraumatic stress disorder: A pilot study. *J Psychological Trauma*. 2008 2008;7(2):122-38.
266. Kiejna A, Pawłowski T, Dudek D, Łojko D, Siwek M, Roczeń R, et al. The utility of Mood Disorder Questionnaire for the detection of bipolar diathesis in treatment-resistant depression. *Journal of Affective Disorders*. 2010;124(3):270-4.
267. Kinrys G, Wygant LE, Pardo TB, Melo M. Levetiracetam for Treatment-Refractory Posttraumatic Stress Disorder. *Journal of Clinical Psychiatry*. 2006 02;67(2):211-4.
268. Kishida I, Aklillu E, Kawanishi C, Bertilsson L, Agren H. Monoamine metabolites level in CSF is related to the 5-HTT gene polymorphism in treatment-resistant depression. *Neuropsychopharmacology*. 2007 10;32(10):2143-51.
269. Klein P, Oertel J. Depression associated with pontine vascular malformation. *Biological Psychiatry*. 1997 09;42(6):519-21.
270. Kocabas NA, Faghel C, Barreto M, Kasper S, Linotte S, Mendlewicz J, et al. The impact of catechol-O-methyltransferase SNPs and haplotypes on treatment response phenotypes in major depressive disorder: A case-control association study. *International Clinical Psychopharmacology*. 2010;25(4):218-27.
271. Kolbinger HM, Höflich G, Hufnagel A, Möller H-J, Kasper S. Transcranial magnetic stimulation (TMS) in the treatment of major depression: A pilot study. *Human Psychopharmacology: Clinical and Experimental*. 1995 Jul-Aug 1995;10(4):305-10.
272. Kosel M, Frick C, Lisanby SH, Fisch H-U, Schlaepfer TE. Magnetic seizure therapy improves mood in refractory major depression. *Neuropsychopharmacology*. 2003 Nov 2003;28(11):2045-8.
273. Kosel M, Sturm V, Frick C, Lenartz D, Zeidler G, Brodesser D, et al. Mood improvement after deep brain stimulation of the internal globus pallidus for tardive dyskinesia in a patient suffering from major depression. *Journal of Psychiatric Research*. 2007 11;41(9):801-3.
274. Koutroumanidis M, Binnie CD, Hennessy MJ, Alarcon G, Elwes RDC, Toone BK, et al. VNS in patients with previous unsuccessful resective epilepsy surgery: Antiepileptic and psychotropic effects. *Acta Neurologica Scandinavica*. 2003 Feb 2003;107(2):117-21.
275. Kozel FA, George MS, Simpson KN. Decision Analysis of Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy for Treatment of Nonpsychotic Severe Depression. *CNS Spectrums*. 2004 Jun 2004;9(6):476-82.
276. Kozel FA, Nahas Z, deBrux C, Molloy M, Lorberbaum JP, Bohning D, et al. How coil-cortex distance relates to age, motor threshold, and antidepressant response to repetitive transcranial magnetic stimulation. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2000 Sum 2000;12(3):376-84.
277. Krahn LE, Gleber E, Rummans TA, Pileggi TS, Lucas DL, Li H. The effects of electroconvulsive therapy on melatonin. *The Journal of ECT*. 2000 12;16(4):391-8.
278. Kraus RP. Pindolol augmentation of tranylcypromine in psychotic depression. *Journal of Clinical Psychopharmacology*. 1997 06;17(3):225-6.
279. Krochmalik A, Jones MK, Menzies RG. Danger Ideation Reduction Therapy (DIRT) for treatment-resistant compulsive washing. *Behaviour Research and Therapy*. 2001 Aug 2001;39(8):897-912.

280. Krymchantowski AV, Jevoux C, Moreira PF. An open pilot study assessing the benefits of quetiapine for the prevention of migraine refractory to the combination of atenolol, nortriptyline, and flunarizine. *Pain Medicine*. 2010;11(1):48-52.
281. Kuipers E, Garety P, Fowler D, Dunn G, Bebbington P, Freeman D, et al. London-East Anglia randomised controlled trial of cognitive-behavioural therapy for psychosis I: Effects of the treatment phase. *British Journal of Psychiatry*. 1997 Oct 1997;171:319-27.
282. Kumagai R, Ichimiya Y. Efficacy of blonanserin in combination therapy for treatment-resistant depression. *Psychiatry and Clinical Neurosciences*. 2009;63(4):593-4.
283. Lam RW, Bartley S, Yatham LN, Tam EM, Zis AP. Clinical predictors of short-term outcome in electroconvulsive therapy. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*. 1999 03;44(2):158-63.
284. Landén M, Björling Gr, Agren H, Fahlén T. A randomized, double-blind, placebo-controlled trial of busiprone in combination with an SSRI in patients with treatment-refractory depression. *Journal of Clinical Psychiatry*. 1998 12;59(12):664-8.
285. Landreville P, Bissonnette L. Effects of cognitive bibliotherapy for depressed older adults with a disability. *Clinical Gerontologist*. 1997 1997;17(4):35-55.
286. Langius-Eklöf A, Samuelsson M. Sense of coherence and psychiatric morbidity in terms of anxiety and depression in patients with major depression before and after electric convulsive treatment. *Scandinavian Journal of Caring Sciences*. 2009;23(2):375-9.
287. Lee J. Potential risks for the off-label use of SSRIs in premature ejaculation. *Journal of Sexual Medicine*. 2010;7(8):2622-4.
288. Lefaucheur J-P, Drouot X, Cunin P, Bruckert R, Lepetit H, Créange A, et al. Motor cortex stimulation for the treatment of refractory peripheral neuropathic pain. *Brain: A Journal of Neurology*. 2009;132(6):1463-71.
289. Lerer B, Isserles M. From Meduna to ultrabrief: New directions for the oldest brain stimulation therapy. *Brain Stimulation*. 2008 Apr 2008;1(2):84-5.
290. Levit-Binnun N, Litvak V, Pratt H, Moses E, Zaroor M, Peled A. Differences in TMS-evoked responses between schizophrenia patients and healthy controls can be observed without a dedicated EEG system. *Clinical Neurophysiology*. 2010;121(3):332-9.
291. Lévy-Rueff M, Gourevitch R, Lôo H, Olié J-P, Amado I. Maintenance electroconvulsive therapy: An alternative treatment for refractory schizophrenia and schizoaffective disorders. *Psychiatry Research*. 2010;175(3):280-3.
292. Leyman L, De Raedt R, Vanderhasselt MA, Baeken C. Influence of high-frequency repetitive transcranial magnetic stimulation over the dorsolateral prefrontal cortex on the inhibition of emotional information in healthy volunteers. *Psychological Medicine: A Journal of Research in Psychiatry and the Allied Sciences*. 2009;39(6):1019-28.
293. Li X, Nahas Z, Anderson B, Kozel FA, George MS. Can left prefrontal rTMS be used as a maintenance treatment for bipolar depression? *Depression and Anxiety*. 2004 2004;20(2):98-100.
294. Liang CS, Yang FW, Chiang KT, Ho PS. Allopurinol for treatment-resistant schizophrenia and epilepsy: A case report. *Pharmacopsychiatry*. 2010;43(6):233-4.
295. Linsen AC, Zitman FG. Patient evaluation of a cognitive behavioral group program for patients with chronic low back pain. *Social Science & Medicine*. 1984 1984;19(12):1361-5.
296. Lisanby SH, Sampson S, Husain MM, Petrides G, Knapp RG, McCall V, et al. Toward individualized post-electroconvulsive therapy care: piloting the Symptom-Titrated, Algorithm-Based Longitudinal ECT (STABLE) intervention. *Journal of ECT*. 2008 Sep 2008;24(3):179-82.

297. Loo C, Mitchell P, Sachdev P, McDarmont B, Parker G, Gandevia S. Double-blind controlled investigation of transcranial magnetic stimulation for the treatment of resistant major depression. *American Journal of Psychiatry*. 1999 Jun 1999;156(6):946-8.
298. Loo CK, Sachdev P, Martin D, Pigot M, Alonzo A, Malhi GS, et al. A double-blind, sham-controlled trial of transcranial direct current stimulation for the treatment of depression. *International Journal of Neuropsychopharmacology*. 2010;13(1):61-9.
299. Luborzewski A, Regen F, Schindler F, Anghelescu I. Modafinil-Induced Reversible Hyperkinetic Nondystonic Movement Disorder in a Patient With Major Depressive Disorder. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2006 Spr;18(2):248-9.
300. MacDonald J, Rawkins S. Neutropenia due to nefazodone, interaction or coincidence? *Australian and New Zealand Journal of Psychiatry*. 2000 12;34(6):1031-2.
301. Mah L, Conn DK. Use of the D2/D3 receptor agonist pramipexole in treatment of rapid-cycling bipolar disorder in an elderly patient. *The American Journal of Geriatric Psychiatry*. 2010;18(3).
302. Mahgoub NA, Kotbi N. Acute depression and suicidal attempt following lowering the frequency of deep brain stimulation. *The Journal of Neuropsychiatry and Clinical Neurosciences*. 2009;21(4).
303. Maletzky B, McFarland B, Burt A. Refractory obsessive compulsive disorder and ECT. *Convulsive Therapy*. 1994 Mar 1994;10(1):34-42.
304. Maluquer SS, Arranz B, San L. Depression improvement with calcium heparin. *General Hospital Psychiatry*. 2002 11;24(6):450-1.
305. Mantovani A, Simpson HB, Fallon BA, Rossi S, Lisanby SH. Randomized sham-controlled trial of repetitive transcranial magnetic stimulation in treatment-resistant obsessive-compulsive disorder. *International Journal of Neuropsychopharmacology*. 2010;13(2):217-27.
306. Marazziti D, Ceraudo G, Consoli G. Effectiveness of duloxetine in a patient suffering from severe panic disorder. *Clinical Neuropsychiatry: Journal of Treatment Evaluation*. 2010;7(1):15-7.
307. Marazziti D, Dell'Osso B. Effectiveness of Risperidone in Psychogenic Stiff Neck. *CNS Spectrums*. 2005 06;10(6):443-4.
308. Marazziti D, Golia F, Consoli G, Presta S, Pfanner C, Carlini M, et al. Effectiveness of long term augmentation with citalopram to clomipramine in treatment-resistance OCD patients. *CNS Spectrums*. 2008 11;13(11):971-6.
309. Margoob MA, Ali Z, Andrade C. Efficacy of ECT in chronic, severe, antidepressant- and CBT-refractory PTSD: An open, prospective study. *Brain Stimulation*. 2010;3(1):28-35.
310. Maron E, Eller T, Vasar V, Nutt DJ. Effects of bupropion augmentation in escitalopram-resistant patients with major depressive disorder: An open-label, naturalistic study. *Journal of Clinical Psychiatry*. 2009;70(7):1054-6.
311. Marshall RD, Johannet CM, Collins PY, Smith H. Bupropion and sertraline combination treatment in refractory depression. *Journal of Psychopharmacology*. 1995;9(3):284-6.
312. Marshall RD, Liebowitz MR. Paroxetine/bupropion combination treatment for refractory depression. *Journal of Clinical Psychopharmacology*. 1996 02;16(1):80-1.
313. Martin M, Crane C. Cognition and the body: Somatic attributions in irritable bowel syndrome. *Behavioural and Cognitive Psychotherapy*. 2003 Jan 2003;31(1):13-31.
314. Martin PG, Butler JE, Gandevia SC, Taylor JL. Noninvasive stimulation of human corticospinal axons innervating leg muscles. *Journal of Neurophysiology*. 2008 Aug 2008;100(2):1080-6.
315. Masaquel A, Wells K, Ettner SL. How does the persistence of depression influence the continuity and type of health insurance and coverage limits on mental health therapy? *Journal of Mental Health Policy and Economics*. 2007 Sep 2007;10(3):133-44.

316. Masdrakis VG, Florakis A, Tzanoulinos G, Markatou M, Oulis P. Safety of the electroconvulsive therapy-ziprasidone combination. *The Journal of ECT*. 2010;26(2):139-42.
317. Mathew SJ, Murrough JW, aan het Rot M, Collins KA, Reich DL, Charney DS. Riluzole for relapse prevention following intravenous ketamine in treatment-resistant depression: A pilot randomized, placebo-controlled continuation trial. *International Journal of Neuropsychopharmacology*. 2010;13(1):71-82.
318. Mattai A, Fung L, Bakalar J, Overman G, Tossell J, Miller R, et al. Adjunctive use of lithium carbonate for the management of neutropenia in clozapine-treated children. *Human Psychopharmacology: Clinical and Experimental*. 2009;24(7):584-9.
319. M'Bailara K, Van den Bulke D, Demazeau N, Demotes-Mainard J, Henry C. Depressive mixed state: Evidence for a new form of depressive state in type I and II bipolar patients. *Neuropsychiatric Disease and Treatment*. 2007;3(6):899-902.
320. McClintock SM, Cullum CM, Husain MM, Rush AJ, Knapp RG, Mueller M, et al. Evaluation of the effects of severe depression on global cognitive function and memory. *CNS Spectrums*. 2010;15(5):304-13.
321. McDonald WM, Easley K, Byrd EH, Holtzheimer P, Tuohy S, Woodard JL, et al. Combination rapid transcranial magnetic stimulation in treatment refractory depression. *Neuropsychiatric Disease and Treatment*. 2006 Jan 2006;2(1):85-94.
322. McIntyre R, Katzman M. The role of atypical antipsychotics in bipolar depression and anxiety disorders. *Bipolar Disorders*. 2003 12;5(2):20-35.
323. McLeod MN, Gaynes BN, Golden RN. Chromium potentiation of antidepressant pharmacotherapy for dysthymic disorder in 5 patients. *Journal of Clinical Psychiatry*. 1999 04;60(4):237-40.
324. McLeod MN, Golden RN. Chromium treatment of depression. *International Journal of Neuropsychopharmacology*. 2000 12;3(4):311-4.
325. McPherson S, Walker C, Caryle J-A. Primary care counsellors' experiences of working with treatment resistant depression: A qualitative pilot study. *Counselling & Psychotherapy Research*. 2006 Dec 2006;6(4):250-7.
326. Medda P, Perugi G, Zanello S, Ciuffa M, Cassano GB. Response to ECT in bipolar I, bipolar II and unipolar depression. *Journal of Affective Disorders*. 2009;118(1-3):55-9.
327. Medda P, Perugi G, Zanello S, Ciuffa M, Rizzato S, Cassano GB. Comparative response to electroconvulsive therapy in medication-resistant bipolar I patients with depression and mixed state. *The Journal of ECT*. 2010;26(2):82-6.
328. Menkes DL, Bodnar P, Ballesteros RA, Swenson MR. Right frontal lobe slow frequency repetitive transcranial magnetic stimulation (SF r-TMS) is an effective treatment for depression: A case-control pilot study of safety and efficacy. *Journal of Neurology, Neurosurgery & Psychiatry*. 1999 Jul 1999;67(1):113-5.
329. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *Journal of Clinical Psychiatry*. 2000 05;61(5):378-81.
330. Messer MM, Haller IV. Maintenance ketamine treatment produces long-term recovery from depression. *Primary Psychiatry*. 2010;17(4):48-50.
331. Michael A, Pallen A, Brown K. Lithium in resistant depression. *Irish Journal of Psychological Medicine*. 1992 May 1992;9(1):71-2.
332. Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Metabolic changes within the left dorsolateral prefrontal cortex occurring with electroconvulsive therapy in patients with treatment resistant unipolar depression. *Psychological Medicine*. 2003 10;33(7):1277-84.
333. Michael N, Gösling M, Reutemann M, Kersting A, Heindel W, Arolt V, et al. Metabolic changes after repetitive transcranial magnetic stimulation (rTMS) of the left prefrontal cortex: a sham-controlled proton magnetic resonance spectroscopy (1H MRS) study of healthy brain. *European Journal of Neuroscience*. 2003 Jun 2003;17(11):2462-8.

334. Mihara K, Nakamura A, Kuba T, Yakushi T, Hotta H, Kojima M, et al. Ropinirole augmentation therapy in a case with treatment-resistant unipolar depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2010;34(4):703-4.
335. Miller IW, Bishop SB, Norman WH, Keitner GI. Cognitive/behavioural therapy and pharmacotherapy with chronic, drug-refractory depressed inpatients: A note of optimism. *Behavioural Psychotherapy*. 1985 Oct 1985;13(4):320-7.
336. Montenegro MA, Guerreiro MM, Scotoni AE, Stella F, Leone Aaaa, Honorato DC, et al. De novo psychogenic seizures after epilepsy surgery: case report. *Arquivos de Neuro-Psiquiatria*. 2000 Jun 2000;58(2):535-7.
337. Moreno FA, Gelenberg AJ, Bachar K, Delgado PL. Pindolol augmentation of treatment-resistant depressed patients. *Journal of Clinical Psychiatry*. 1997 10;58(10):437-9.
338. Morgan JF, Crisp AH. Use of leukotomy for intractable anorexia nervosa: A long-term follow-up study. *International Journal of Eating Disorders*. 2000 Apr 2000;27(3):249-58.
339. Morishita S, Aoki S. Clonazepam in the treatment of prolonged depression. *Journal of Affective Disorders*. 1999 06;53(3):275-8.
340. Morishita S, Arita S. Lithium Augmentation of Antidepressants in the Treatment of Protracted Depression. *International Medical Journal*. 2003 03;10(1):29-32.
341. Morishita S, Sonohara M, Murakami H, Matsushita K, Ebata J, Koshikawa T, et al. Vitamin E treatment of prolonged depression: A report of nine cases. *International Medical Journal*. 2000 03;7(1):33-6.
342. Moscrip TD, Terrace HS, Sackeim HA, Lisanby SH. Randomized controlled trial of the cognitive side-effects of magnetic seizure therapy (MST) and electroconvulsive shock (ECS). *International Journal of Neuropsychopharmacology*. 2006 Feb 2006;9(1):1-11.
343. Mottaghy FM, Keller CE, Gangitano M, Ly J, Thall M, Parker JA, et al. Correlation of cerebral blood flow and treatment effects of repetitive transcranial magnetic stimulation in depressed patients. *Psychiatry Research: Neuroimaging*. 2002 Aug 2002;115(1):1-14.
344. Mueller PS, Albin SM, Barnes RD, Rasmussen KG, Jr. Safety of electroconvulsive therapy in patients With unrepaired abdominal aortic aneurysm: Report of 8 patients. *The Journal of ECT*. 2009;25(3):165-9.
345. Müller JF, Orekhov Y, Liu Y, Ziemann U. Homeostatic plasticity in human motor cortex demonstrated by two consecutive sessions of paired associative stimulation. *European Journal of Neuroscience*. 2007 Jun 2007;25(11):3461-8.
346. Müller K, Fabó D, Entz L, Kelemen A, Halász P, Rásonyi G, et al. Outcome of vagus nerve stimulation for epilepsy in Budapest. *Epilepsia*. 2010;51(Suppl 3):98-101.
347. Müller UJ, Sturm V, Voges J, Heinze HJ, Galazky I, Heldmann M, et al. Successful treatment of chronic resistant alcoholism by deep brain stimulation of nucleus accumbens: First experience with three cases. *Pharmacopsychiatry*. 2009;42(6):288-91.
348. Müller-Dahlhaus JF, Liu Y, Ziemann U. Interindividual variability and age-dependency of motor cortical plasticity induced by paired associative stimulation. *Experimental Brain Research*. 2008 May 2008;187(3):467-75.
349. Münchau A, Bloem BR, Thilo KV, Trimble MR, Rothwell JC, Robertson MM. Repetitive transcranial magnetic stimulation for Tourette syndrome. *Neurology*. 2002 Dec 2002;59(11):1789-91.
350. Münchau A, Langosch JM, Gerschlag W, Rothwell JC, Orth M, Trimble MR. Mirtazapine increases cortical excitability in healthy controls and epilepsy patients with major depression. *Journal of Neurology, Neurosurgery & Psychiatry*. 2005 Apr 2005;76(4):527-33.

351. Murakami T, Sakuma K, Nomura T, Uemura Y, Hashimoto I, Nakashima K. Changes in somatosensory-evoked potentials and high-frequency oscillations after paired-associative stimulation. *Experimental Brain Research*. 2008 Jan 2008;184(3):339-47.
352. Nagler J. Absence of asystole during bifrontal stimulation in electroconvulsive therapy. *The Journal of ECT*. 2010;26(2):100-3.
353. Nahas Z, Anderson BS, Borckardt J, Arana AB, George MS, Reeves ST, et al. Bilateral epidural prefrontal cortical stimulation for treatment-resistant depression. *Biological Psychiatry*. 2010;67(2):101-9.
354. Nahas Z, Bohning DE, Molloy MA, Oustz JA, Risch SC, George MS. Safety and feasibility of repetitive transcranial magnetic stimulation in the treatment of anxious depression in pregnancy: A case report. *Journal of Clinical Psychiatry*. 1999 Jan 1999;60(1):50-2.
355. Nahas Z, Teneback CC, Kozel A, Speer AM, DeBrux C, Molloy M, et al. Brain effects of TMS delivered over prefrontal cortex in depressed adults: Role of stimulation frequency and coil-cortex distance. *Journal of Neuropsychiatry & Clinical Neurosciences*. 2001 Fal 2001;13(4):459-70.
356. Nakajima S, Ishida T, Akaishi R, Takahata K, Kitahata R, Uchida H, et al. Impacts of switching antidepressants after successful electroconvulsive therapy on the maintenance of clinical remission in patients with treatment-resistant depression: A chart review. *The Journal of ECT*. 2009;25(3):178-81.
357. Neuner I, Halfter S, Wollenweber F, Podoll K, Schneider F. Nucleus accumbens deep brain stimulation did not prevent suicide attempt in Tourette syndrome. *Biological Psychiatry*. 2010;68(4):e19-e20.
358. Ng RMK. Cognitive Therapy for Obsessive-compulsive Personality Disorder - A Pilot Study in Hong Kong Chinese Patients. *Hong Kong J Psychiatry*. 2005 Jun 2005;15(2):50-3.
359. Ng RMK, Hui LK, Pau L. Cognitive-behavioural therapy by novices for supervised community hostel residents with treatment-resistant schizophrenia in Hong Kong: A pilot study. *Hong Kong J Psychiatry*. 2008 Jun 2008;18(2):49-54.
360. Nicolato R, Dias FvF, Salgado JoVc, Cardoso Vale RD, Teixeira AnLc. Diagnostic and therapeutic challenges involving patients with post-traumatic stress disorder and schizoaffective disorder depressive type. *Acta Neuropsychiatrica*. 2009 02;21(1):47-8.
361. Nierenberg AA, Fava M, Trivedi MH, Wisniewski SR, Thase ME, McGrath PJ, et al. Comparison of Lithium and T(3) Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report. *The American Journal of Psychiatry*. 2006 09;163(9):1519-30.
362. Nilsson BM, Ekselius L. Acute and maintenance electroconvulsive therapy for treatment of severely disabling obsessive-compulsive symptoms in a patient with Asperger Syndrome. *The Journal of ECT*. 2009;25(3):205-7.
363. No authorship i. Feature Interview: David Avery, MD on Transcranial Magnetic Stimulation for depression. *Essential Psychopharmacology*. 2004 2004;5(4):307-14.
364. No authorship i. Botox treatment of depression. *Primary Psychiatry*. 2006 Jul 2006;13(7):26-7.
365. Noble JM. Religious coping styles, perceived stress, depression, and professional psychological help-seeking attitudes among African American women. *Dissertation Abstracts International Section A: Humanities and Social Sciences*. 1998 Apr 1998;58(10):3743.
366. Nordanskog P, Dahlstrand U, Larsson MR, Larsson E-M, Knutsson L, Johanson A. Increase in hippocampal volume after electroconvulsive therapy in patients with depression: A volumetric magnetic resonance imaging study. *The Journal of ECT*. 2010;26(1):62-7.

367. Ntatsaki E, D'Mello O, Lewis J, Underwood BR, Smith M, Head L. Electroconvulsive treatment for a patient with psychotic depression and inclusion body myositis. *The Journal of ECT*. 2009;25(2):125-8.
368. Oathes DJ, Bruce JM, Nitschke JB. Worry facilitates corticospinal motor response to transcranial magnetic stimulation. *Depression and Anxiety*. 2008;25(11):969-76.
369. O'Connor DW, Gardner B, Presnell I, Singh D, Tsanglis M, White E. The effectiveness of continuation-maintenance ECT in reducing depressed older patients' hospital re-admissions. *Journal of Affective Disorders*. 2010;120(1-3):62-6.
370. Ogden M, Lyndon W, Pridmore S. Repetitive transcranial magnetic stimulation (rTMS) in major depressive episode with postpartum onset: A case study. *German J Psychiatry*. 1999;2(1):43-5.
371. Okada F, Okajima K. Violent acts associated with fluvoxamine treatment. *Journal of Psychiatry & Neuroscience*. 2001;26(4):339-40.
372. Okamoto N, Furusawa Y, Sakamoto K, Yamamoto T, Kondo Y, Nagafusa Y, et al. Major depression: What caused the crisis? *The Lancet*. 2010;375(9711).
373. Okamoto N, Nakai T, Sakamoto K, Nagafusa Y, Higuchi T, Nishikawa T. Rapid antidepressant effect of ketamine anesthesia during electroconvulsive therapy of treatment-resistant depression: Comparing ketamine and propofol anesthesia. *The Journal of ECT*. 2010;26(3):223-7.
374. Okamoto N, Sakamoto K, Nagafusa Y, Ichikawa M, Nakai T, Higuchi T. Electroconvulsive therapy as a potentially effective treatment for severe serotonin syndrome: Two case reports. *Journal of Clinical Psychopharmacology*. 2010;30(3):350-1.
375. Okazaki M, Tominaga K, Higuchi H, Utagawa I, Nakamura E, Noguchi M, et al. Predictors of response to electroconvulsive therapy obtained using the three-factor structure of the Montgomery and Åsberg Depression Rating Scale for treatment-resistant depressed patients. *The Journal of ECT*. 2010;26(2):87-90.
376. O'Reardon JP, Blumner KH, Peshek AD, Pradilla RR, Pimienta PC. Long-Term Maintenance Therapy for Major Depressive Disorder With rTMS. *Journal of Clinical Psychiatry*. 2005 Dec 2005;66(12):1524-8.
377. O'Reardon JP, Fontecha JF, Cristancho MA, Newman S. Unexpected reduction in migraine and psychogenic headaches following rTMS treatment for major depression: A report of two cases. *CNS Spectrums*. 2007 Dec 2007;12(12):921-5.
378. Ostroff RB, Nelson JC. Risperidone augmentation of selective serotonin reuptake inhibitors in major depression. *Journal of Clinical Psychiatry*. 1999 04;60(4):256-9.
379. Oulis P, Kokras N, Papadimitriou GN, Masdrakis VG. Adjunctive low-dose amisulpride in motor conversion disorder. *Clinical neuropharmacology*. 2009;32(6):342-3.
380. Pérez V, Soler J, Puidgemont D, Alvarez E, Artigas F. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Archives of General Psychiatry*. 1999 04;56(4):375-9.
381. Padberg F, di Michele F, Zwanzger P, Romeo E, Bernardi G, Schüle C, et al. Plasma concentrations of neuroactive steroids before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. *Neuropsychopharmacology*. 2002 Nov 2002;27(5):874-8.
382. Padberg F, di Michele F, Zwanzger P, Romeo E, Bernardi G, Schüle C, et al. Plasma concentrations of neuroactive steroids before and after repetitive transcranial magnetic stimulation in depression: Correction. *Neuropsychopharmacology*. 2003 Mar 2003;28(3):610-1.
383. Palmio J, Huuhka M, Laine S, Huhtala H, Peltola J, Leinonen E, et al. Electroconvulsive therapy and biomarkers of neuronal injury and plasticity: Serum levels of neuron-specific enolase and S-100b protein. *Psychiatry Research*. 2010;177(1-2):97-100.

384. Papakostas GI, Petersen T, Iosifescu DV, Burns AM, Nierenberg AA, Alpert JE, et al. Obesity among outpatients with major depressive disorder. *International Journal of Neuropsychopharmacology*. 2005 03;8(1):59-63.
385. Papakostas GI, Petersen T, Mischoulon D, Hughes ME, Spector AR, Alpert JE, et al. Functioning and interpersonal relationships as predictors of response in treatment-resistant depression. *Comprehensive Psychiatry*. 2003 01;44(1):44-50.
386. Papakostas GI, Petersen T, Pava J, Masson E, Worthington JJ, III, Alpert JE, et al. Hopelessness and Suicidal Ideation in Outpatients With Treatment-Resistant Depression: Prevalence and Impact on Treatment Outcome. *Journal of Nervous and Mental Disease*. 2003 07;191(7):444-9.
387. Papakostas GI, Petersen T, Sonawalla SB, Merens W, Iosifescu DV, Alpert JE, et al. Serum cholesterol in treatment-resistant depression. *Neuropsychobiology*. 2003;47(3):146-51.
388. Papakostas GI, Petersen TJ, Kinrys G, Burns AM, Worthington JJ, III, Alpert JE, et al. Aripiprazole Augmentation of Selective Serotonin Reuptake Inhibitors for Treatment-Resistant Major Depressive Disorder. *Journal of Clinical Psychiatry*. 2005 10;66(10):1326-30.
389. Papakostas GI, Petersen TJ, Nierenberg AA, Murakami JL, Alpert JE, Rosenbaum JF, et al. Ziprasidone augmentation of selective serotonin reuptake inhibitors (SSRIs) for SSRI-resistant major depressive disorder. *Journal of Clinical Psychiatry*. 2004 02;65(2):217-21.
390. Parker G, Brotchie H. Do the old psychostimulant drugs have a role in managing treatment-resistant depression? *Acta Psychiatrica Scandinavica*. 2010;121(4):308-14.
391. Parker G, Watkins T. Treatment-resistant depression: When antidepressant drug intolerance may indicate food intolerance. *Australian and New Zealand Journal of Psychiatry*. 2002 04;36(2):263-5.
392. Paslakis G, Gilles M, Deuschle M. Clinically relevant pharmacokinetic interaction between venlafaxine and bupropion: A case series. *Journal of Clinical Psychopharmacology*. 2010;30(4):473-4.
393. Pasquini M, Berardelli I, Biondi M. Amantadine augmentation for refractory obsessive-compulsive disorder: A case report. *Journal of Clinical Psychopharmacology*. 2010;30(1):85-6.
394. Pathak S, Johns ES, Kowatch RA. Adjunctive Quetiapine for Treatment-Resistant Adolescent Major Depressive Disorder: A Case Series. *Journal of Child and Adolescent Psychopharmacology*. 2005 Sep 2005;15(4):696-702.
395. Patkar AA, Masand PS, Pae C-U, Peindl K, Hooper-Wood C, Mannelli P, et al. A Randomized, Double-blind, Placebo-controlled Trial of Augmentation with an Extended Release Formulation of Methylphenidate in Outpatients with Treatment-Resistant Depression. *Journal of Clinical Psychopharmacology*. 2006 12;26(6):653-6.
396. Peet M, Horrobin DF. A dose-ranging study of the effects of ethyl-eicosapentaenoate in patients with ongoing depression despite apparently adequate treatment with standard drugs. *Archives of General Psychiatry*. 2002 10;59(10):913-20.
397. Perez MA, Lundbye-Jensen J, Nielsen JB. Task-specific depression of the soleus H-reflex after contraction training of antagonistic ankle muscles. *Journal of Neurophysiology*. 2007 Dec 2007;98(6):3677-87.
398. Perkins C, Jr. Aripiprazole effective as adjunct to antidepressant therapy in patients with major depressive disorder. *Primary Psychiatry*. 2007 07;14(7):18-.
399. Perretti A, Balbi P, Orefice G, Trojano L, Marcantonio L, Brescia-Morra V, et al. Post-exercise facilitation and depression of motor evoked potentials to transcranial magnetic stimulation: A study in multiple sclerosis. *Clinical Neurophysiology*. 2004 Sep 2004;115(9):2128-33.

400. Perugi G, Frare F, Toni C, Tusini G, Vannucchi G, Akiskal HS. Adjunctive valproate in panic disorder patients with comorbid bipolar disorder or otherwise resistant to standard antidepressants: A 3-year "open" follow-up study. *European Archives of Psychiatry and Clinical Neuroscience*. 2010;260(7):553-60.
401. Pesiridou A, Baquero G, Cristancho P, Wakil L, Altinay M, Kim D, et al. A case of delayed onset of threatened premature labor in association with electroconvulsive therapy in the third trimester of pregnancy. *The Journal of ECT*. 2010;26(3):228-30.
402. Petajan JH, White AT. Motor-evoked potentials in response to fatiguing grip exercise in multiple sclerosis patients. *Clinical Neurophysiology*. 2000 Dec 2000;111(12):2188-95.
403. Petersen T, Hughes M, Papakostas GI, Kant A, Fava M, Rosenbaum JF, et al. Treatment-resistant depression and Axis II comorbidity. *Psychotherapy and Psychosomatics*. 2002 Sep-Oct 2002;71(5):269-74.
404. Petersen T, Papakostas GI, Mahal Y, Guyker WM, Beaumont EC, Alpert JE, et al. Psychosocial functioning in patients with treatment resistant depression. *European Psychiatry*. 2004 06;19(4):196-201.
405. Peterson TJ, Feldman G, Harley R, Fresco DM, Graves L, Holmes A, et al. Extreme response style in recurrent and chronically depressed patients: Change with antidepressant administration and stability during continuation treatment. *Journal of Consulting and Clinical Psychology*. 2007 Feb 2007;75(1):145-53.
406. Phelps LE, Brutsche N, Moral JR, Luckenbaugh DA, Manji HK, Zarate CA, Jr. Family history of alcohol dependence and initial antidepressant response to an N-methyl-D-aspartate antagonist. *Biological Psychiatry*. 2009 01;65(2):181-4.
407. Philip NS, Carpenter LL, Tyrka AR, Price LH. Using atypical antipsychotics to augment treatment of nonpsychotic unipolar major depression. *Directions in Psychiatry*. 2009;29(1):51-8.
408. Philip NS, Carpenter LL, Tyrka AR, Whiteley LB, Price LH. Varenicline augmentation in depressed smokers: An 8-week, open-label study. *Journal of Clinical Psychiatry*. 2009 07;70(7):1026-31.
409. Picardi A, Di Gennaro G, Meldolesi GN, Grammaldo LG, Esposito V, Quarato PP. Partial Seizures due to Sclerosis of the Right Amygdala Presenting as Panic Disorder. *Psychopathology*. 2007 2007;40(3):178-83.
410. Piccinni A, Del Debbio A, Medda P, Bianchi C, Roncaglia I, Veltri A, et al. Plasma brain-derived neurotrophic factor in treatment-resistant depressed patients receiving electroconvulsive therapy. *European Neuropsychopharmacology*. 2009 05;19(5):349-55.
411. Pieroni S, McShane R. Effect of an educational video on the accuracy of surrogate decisions: The case of electroconvulsive therapy. *The Journal of ECT*. 2010;26(3):208-12.
412. Pilhatsch MK, Burghardt R, Wandinger KP, Bauer M, Adli M. Augmentation with atomoxetine in treatment-resistant depression with psychotic features: A case report. *Pharmacopsychiatry*. 2006 03;39(2):79-80.
413. Pinto A, La Pia S, Mennella R, Giorgio D, DeSimone L. Cognitive-behavioral therapy and clozapine for clients with treatment-refractory schizophrenia. *Psychiatric Services*. 1999 Jul 1999;50(7):901-4.
414. Pitcher JB, Ridding MC, Miles TS. Frequency-dependent, bi-directional plasticity in motor cortex of human adults. *Clinical Neurophysiology*. 2003 Jul 2003;114(7):1265-71.
415. Pogarell O, Koch W, Pöpperl G, Tatsch K, Jakob F, Zwanzger P, et al. Striatal dopamine release after prefrontal repetitive transcranial magnetic stimulation in major depression: preliminary results of a dynamic [¹²³I] IBZM SPECT study. *Journal of Psychiatric Research*. 2006 Jun 2006;40(4):307-14.
416. Pomara N, Gershon S. Treatment-resistant depression in an elderly patient with pancreatic carcinoma: Case report. *Journal of Clinical Psychiatry*. 1984 10;45(10):439-40.

417. Poon DE, Roy FD, Gorassini MA, Stein RB. Interaction of paired cortical and peripheral nerve stimulation on human motor neurons. *Experimental Brain Research*. 2008 Jun 2008;188(1):13-21.
418. Porta M, Brambilla A, Cavanna AE, Servello D, Sassi M, Rickards H, et al. Thalamic deep brain stimulation for treatment-refractory Tourette syndrome: Two-year outcome. *Neurology*. 2009;73(17):1375-80.
419. Porter R, Booth D, Gray H, Frampton C. Effects of the addition of remifentanyl to propofol anesthesia on seizure length and postictal suppression index in electroconvulsive therapy. *Journal of ECT*. 2008 Sep 2008;24(3):203-7.
420. Poulet E, Brunelin J, Ben Makhlof W, D'Amato T, Saoud M. A case report of cTBS for the treatment of auditory hallucinations in a patient with schizophrenia. *Brain Stimulation*. 2009;2(2):118-9.
421. Prakash J, Kotwal A, Prabhu HRA. Therapeutic and Prophylactic Utility of the Memory-Enhancing Drug Donepezil Hydrochloride on Cognition of Patients Undergoing Electroconvulsive Therapy: A Randomized Controlled Trial. *Journal of ECT*. 2006 Sep 2006;22(3):163-8.
422. Preskorn SH. Polypharmacy in a patient with refractory major depression. Part I: The case. *Journal of Psychiatric Practice*. 2002 11;8(6):370-6.
423. Preskorn SH. Polypharmacy in a case of refractory major depression: Part II: Implications for clinical management. *Journal of Psychiatric Practice*. 2003 01;9(1):71-8.
424. Price RB, Shungu DC, Mao X, Nestadt P, Kelly C, Collins KA, et al. Amino acid neurotransmitters assessed by proton magnetic resonance spectroscopy: Relationship to treatment resistance in major depressive disorder. *Biological Psychiatry*. 2009 05;65(9):792-800.
425. Pridmore S, Bruno R, Turnier-Shea Y, Reid P, Rybak M. Comparison of unlimited numbers of rapid transcranial magnetic stimulation (rTMS) and ECT treatment sessions in major depressive episode. *International Journal of Neuropsychopharmacology*. 2000 Jun 2000;3(2):129-34.
426. Pridmore S, Poxon M, Chan C. Longer than expected course of transcranial magnetic stimulation. *Australian and New Zealand Journal of Psychiatry*. 1998 Feb 1998;32(1):140.
427. Pridmore S, Rybak M, Turnier-Shea Y, Reid P, Bruno PR, Couper D. A naturalistic study of response in melancholia to transcranial magnetic stimulation (TMS). *German Journal of Psychiatry*. 1999 1999;2(1):13-21.
428. Puri BK, Counsell SJ, Richardson AJ, Horrobin DF. Eicosapentaenoic acid in treatment-resistant depression. *Archives of General Psychiatry*. 2002 01;59(1):91-2.
429. Quitkin F, McGrath PJ, Stewart JW, Ocepek-Welikson K, Taylor BP, Nunes E, et al. Chronological milestones to guide drug change: When should clinicians switch antidepressants? *Archives of General Psychiatry*. 1996 09;53(9):785-92.
430. Raja M. Delayed loss of efficacy and depressogenic action of antidepressants. *Journal of Clinical Psychopharmacology*. 2009;29(6):612-4.
431. Rasmussen KG, Stevens SR, Kung S, Mohan A. Melancholic symptoms as assessed by the Hamilton Depression Rating Scale and outcomes with and without electroconvulsive therapy on an in-patient mood disorders unit. *Acta Neuropsychiatrica*. 2010;22(1):21-5.
432. Reda MA, Carpinello B, Secchiaroli L, Blanco S. Thinking, depression, and antidepressants: Modified and unmodified depressive beliefs during treatment with amitriptyline. *Cognitive Therapy and Research*. 1985 Apr 1985;9(2):135-43.
433. Reid P, Pridmore S. Improvement in chronic pain with transcranial magnetic stimulation. *Australian and New Zealand Journal of Psychiatry*. 2001 Apr 2001;35(2):252.

434. Reid PD, Daniels B, Rybak M, Turnier-Shea Y, Pridmore S. Cortical excitability of psychiatric disorders: Reduced post-exercise facilitation in depression compared to schizophrenia and controls. *Australian and New Zealand Journal of Psychiatry*. 2002 Oct 2002;36(5):669-73.
435. Reid PD, Pridmore S. Dexamethasone suppression test reversal in rapid transcranial magnetic stimulation-treated depression. *Australian and New Zealand Journal of Psychiatry*. 1999 Apr 1999;33(2):274-7.
436. Reif A, Leonhard C, Mössner R, Lesch K-P, Fallgatter AJ. Encephalopathy and myoclonus triggered by valproic acid. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2004 09;28(6):1061-3.
437. Richter J, Möller B, Spitzer C, Letzel S, Bartols S, Barnow S, et al. Transcallosal inhibition in patients with and without alexithymia. *Neuropsychobiology*. 2006 Apr 2006;53(2):101-7.
438. Rim CL, Gitlin MJ. Ziprasidone, monoamine oxidase inhibitors, and the serotonin syndrome. *Journal of Clinical Psychopharmacology*. 2010;30(4):470-1.
439. Riva G, Bacchetta M, Cesa G, Conti S, Molinari E. Six-Month Follow-Up of In-Patient Experiential Cognitive Therapy for Binge Eating Disorders. *CyberPsychology & Behavior*. 2003 Jun 2003;6(3):251-8.
440. Rollnik JD, Huber TJ, Mogk H, Siggelkow S, Kropp S, Dengler R, et al. High frequency repetitive transcranial magnetic stimulation (rTMS) of the dorsolateral prefrontal cortex in schizophrenic patients. *Neuroreport: For Rapid Communication of Neuroscience Research*. 2000 Dec 2000;11(18):4013-5.
441. Ropohl A, Hiller M, Elstner S, Sperling W, Kornhuber J, Bickel A. Dental pain during repetitive transcranial magnetic stimulation. *European Psychiatry*. 2004 Nov 2004;19(7):457-8.
442. Rosa MA, Picarelli H, Teixeira MJ, Rosa MO, Marcolin MA. Accidental seizure with repetitive transcranial magnetic stimulation. *Journal of ECT*. 2006 Dec 2006;22(4):265-6.
443. Rosenhagen MC, Uhr M. Single nucleotide polymorphism in the drug transporter gene ABCB1 in treatment-resistant depression: Clinical practice. *Journal of Clinical Psychopharmacology*. 2010;30(2):209-11.
444. Rosenkranz K, Williamon A, Rothwell JC. Motorcortical excitability and synaptic plasticity is enhanced in professional musicians. *Journal of Neuroscience*. 2007 May 2007;27(19):5200-6.
445. Rothbaum BO, Killeen TK, Davidson JRT, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2008 04;69(4):520-5.
446. Rothschild AJ. The diagnosis and treatment of late-life depression. *Journal of Clinical Psychiatry*. 1996 1996;57(5):5-11.
447. Rush AJ, Kilner J, Fava M, Wisniewski SR, Warden D, Nierenberg AA, et al. Clinically relevant findings from STAR*D. *Psychiatric Annals*. 2008 03;38(3):188-93.
448. Russell JC, Rasmussen KG, O'Connor MK, Copeman CA, Ryan DA, Rummans TA. Long-term maintenance ECT: A retrospective review of efficacy and cognitive outcome. *Journal of ECT*. 2003 2003;19(1):4-9.
449. Ruzek JI, Riney SJ, Leskin G, Drescher KD, Foy DW, Gusman FD. Do post-traumatic stress disorder symptoms worsen during trauma focus group treatment? *Military Medicine*. 2001 Oct 2001;166(10):898-902.
450. Rybak M, Bruno R, Turnier-Shea Y, Pridmore S. An attempt to increase the rate and magnitude of the antidepressant effect of transcranial magnetic stimulation (TMS) a pilot study. *German Journal of Psychiatry*. 2005 2005;8(4):59-65.
451. Rybakowski JK, Angst J, Dudek D, Pawlowski T, Lojko D, Siwek M, et al. Polish version of the Hypomania Checklist (HCL-32) scale: The results in treatment-resistant depression. *European Archives of Psychiatry and Clinical Neuroscience*. 2010;260(2):139-44.

452. Saba G, Verdon CM, Kalalou K, Rocamora JF, Dumortier G, Benadhira R, et al. Transcranial magnetic stimulation in the treatment of schizophrenic symptoms: A double blind sham controlled study. *Journal of Psychiatric Research*. 2006 Mar 2006;40(2):147-52.
453. Sachdev PS, Loo CK, Mitchell PB, McFarquhar TF, Malhi GS. Repetitive transcranial magnetic stimulation for the treatment of obsessive compulsive disorder: A double-blind controlled investigation. *Psychological Medicine*. 2007 Nov 2007;37(11):1645-9.
454. Sachsse U, Vogel C, Leichsenring F. Results of psychodynamically oriented trauma-focused inpatient treatment for women with complex posttraumatic stress disorder (PTSD) and borderline personality disorder (BPD). *Bulletin of the Menninger Clinic*. 2006 Spr 2006;70(2):125-44.
455. Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, et al. Effect of electroconvulsive therapy on 5-HT_{1A} receptor binding in patients with depression: A PET study with [¹¹C]WAY 100635. *International Journal of Neuropsychopharmacology*. 2010;13(6):785-91.
456. Sakkas P, Mihalopoulou P, Mourtzouhou P, Psarros C, Masdrakis V, Politis A, et al. Induction of mania by rTMS: report of two cases. *European Psychiatry*. 2003 Jun 2003;18(4):196-8.
457. Sakkas P, Psarros C, Papadimitriou GN, Theleritis CG, Soldatos CR. Repetitive transcranial magnetic stimulation (rTMS) in a patient suffering from comorbid depression and panic disorder following a myocardial infarction. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2006 Jul 2006;30(5):960-2.
458. Salloum IM, Cornelius JR, Thase ME, Daley DC, Kirisci L, Spotts C. Naltrexone utility in depressed alcoholics. *Psychopharmacology Bulletin*. 1998;34(1):111-5.
459. Samii A, Wassermann EM, Hallett M. Post-exercise depression of motor evoked potentials as a function of exercise duration. *Electroencephalography & Clinical Neurophysiology: Electromyography & Motor Control*. 1997 Oct 1997;105(5):352-6.
460. Samii A, Wassermann EM, Ikoma K, Mercurim B. Decreased postexercise facilitation of motor evoked potentials in patients with chronic fatigue syndrome or depression. *Neurology*. 1996 Dec 1996;47(6):1410-4.
461. Santoro A, Florita M, Rossini D, Benedetti F, Lucca A. The processing of emotional stimuli in subjects with a major depression episode treated with rTMS. *Clinical Neuropsychiatry: Journal of Treatment Evaluation*. 2005 Jun 2005;2(3):183-8.
462. Sarkhel S, Sinha VK, Praharaj SK. Adjunctive high-frequency right prefrontal repetitive transcranial magnetic stimulation (rTMS) was not effective in obsessive-compulsive disorder but improved secondary depression. *Journal of Anxiety Disorders*. 2010;24(5):535-9.
463. Sartorius A, Kiening KL, Kirsch P, von Gall CC, Haberkorn U, Unterberg AW, et al. Remission of major depression under deep brain stimulation of the lateral habenula in a therapy-refractory patient. *Biological Psychiatry*. 2010;67(2):e9-e11.
464. Schlaepfer TE, Cohen MX, Frick C, Kosel M, Brodessa D, Axmacher N, et al. Deep brain stimulation to reward circuitry alleviates anhedonia in refractory major depression. *Neuropsychopharmacology*. 2008 Jan 2008;33(2):368-77.
465. Schneier FR, Belzer KD, Kishon R, Amsel L, Simpson HB. Escitalopram for persistent symptoms of generalized anxiety disorder after CBT: A pilot study. *Journal of Nervous and Mental Disease*. 2010;198(6):458-61.
466. Schrader GD, Levien HE. Response to sequential administration of clomipramine and lithium carbonate in treatment-resistant depression. *British Journal of Psychiatry*. 1985 11;147:573-5.

467. Schramm E, Schneider D, Zobel I, van Calker D, Dykieriek P, Kech S, et al. Efficacy of interpersonal psychotherapy plus pharmacotherapy in chronically depressed inpatients. *Journal of Affective Disorders*. 2008 Jul 2008;109(1):65-73.
468. Schutter DJLG, van Honk J, Laman M, Vergouwen AC, Koerselman F. Increased sensitivity for angry faces in depressive disorder following 2 weeks of 2-Hz repetitive transcranial magnetic stimulation to the right parietal cortex. *International Journal of Neuropsychopharmacology*. 2010;13(9):1155-61.
469. Schwartz TL, Costello A. Charting a sustained response to vagus nerve stimulation in treatment-resistant major depressive disorder. *Primary Psychiatry*. 2007 Aug 2007;14(8):66-8.
470. Scocco P, Frank E. Interpersonal psychotherapy as augmentation treatment in depressed elderly responding poorly to antidepressant drugs: A case series. *Psychotherapy and Psychosomatics*. 2002 Nov-Dec 2002;71(6):357-61.
471. Seidman SN, Miyazaki M, Roose SP. Intramuscular testosterone supplementation to selective serotonin reuptake inhibitor in treatment-resistant depressed men: Randomized placebo-controlled clinical trial. *Journal of Clinical Psychopharmacology*. 2005 12;25(6):584-8.
472. Sengul C, Kalkanci Ö, Simsek D, Herken H. Maintenance electroconvulsive therapy combined with long-acting risperidone in the treatment of resistant bipolar affective disorder. *The Journal of ECT*. 2009;25(4):282-3.
473. Serby M. Methylphenidate-Induced Obsessive-Compulsive Symptoms in an Elderly Man. *CNS Spectrums*. 2003 08;8(8):612-3.
474. Serby MJ, Lantz M, Chabus BI, Bernay LJ. Takotsubo cardiomyopathy and electroconvulsive treatments: A case study and review. *International Journal of Psychiatry in Medicine*. 2010;40(1):93-6.
475. Seymour J, Wattis JP. Treatment resistant depression in the elderly: Three cases. *International Clinical Psychopharmacology*. 1992 Spr;7(1):55-7.
476. Shah A. The impact of the National Institute of Clinical Excellence guidance on the use of electroconvulsive therapy in England. *International Psychogeriatrics*. 2010;22(1):164-6.
477. Shajahan PM, Glabus MF, Jenkins JA, Ebmeier KP. Postexercise motor evoked potentials in depressed and recovered depressed patients, and controls. *Neurology*. 1999 Aug 1999;53(3):644-6.
478. Shajahan PM, Glabus MF, Steele JD, Doris AB, Anderson K, Jenkins JA, et al. Left dorso-lateral repetitive transcranial magnetic stimulation affects cortical excitability and functional connectivity, but does not impair cognition in major depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2002 Jun 2002;26(5):945-54.
479. Shanmugham B, Karp J, Drayer R, Reynolds CF, III, Alexopoulos G. Evidence-based pharmacologic interventions for geriatric depression. *Psychiatric Clinics of North America*. 2005 Dec 2005;28(4):821-35.
480. Sharma V, Khan M. Identification of bipolar disorder in women with postpartum depression. *Bipolar Disorders*. 2010;12(3):335-40.
481. Sharma V, Khan M, Corpse C. Role of lamotrigine in the management of treatment-resistant bipolar II depression: A chart review. *Journal of Affective Disorders*. 2008 11;111(1):100-5.
482. Shields DC, Asaad W, Eskandar EN, Jain FA, Cosgrove GR, Flaherty AW, et al. Prospective assessment of stereotactic ablative surgery for intractable major depression. *Biological Psychiatry*. 2008 09;64(6):449-54.
483. Shteinlukht T. Review of 'Electroconvulsive therapy: A guide for professionals and their patients'. *Psychiatric Services*. 2009;60(9).
484. Siddiqui F, Herial NA, Ali II. Cumulative effect of vagus nerve stimulators on intractable seizures observed over a period of 3 years. *Epilepsy & Behavior*. 2010;18(3):299-302.

485. Sidhoumi D, Braha S, Bouaziz N, Brunelin J, Benadhira R, Januel D. Evaluation of the therapeutic effect of theta burst stimulation on drug-resistant auditory hallucinations in a schizophrenic patient and its impact on cognitive function and neuronal excitability: A case study. *Clinical Neurophysiology*. 2010;121(5).
486. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: Clinical efficacy. *Journal of Affective Disorders*. 2009;116(1-2):106-12.
487. Simon NM, Connor KM, LeBeau RT, Hoge EA, Worthington JJ, III, Zhang W, et al. Quetiapine augmentation of paroxetine CR for the treatment of refractory generalized anxiety disorder: Preliminary findings. *Psychopharmacology*. 2008 05;197(4):675-81.
488. Siwek M, Dudek D, Paul IA, Sowa-Kućma M, Zięba A, Popik P, et al. Zinc supplementation augments efficacy of imipramine in treatment resistant patients: A double blind, placebo-controlled study. *Journal of Affective Disorders*. 2009 11;118(1):187-95.
489. Siwek M, Dudek D, Schlegel-Zawadzka M, Morawska A, Piekoszewski W, Opoka W, et al. Serum zinc level in depressed patients during zinc supplementation of imipramine treatment. *Journal of affective disorders*. 2010;126(3):447-52.
490. Sjögren MJ, Hellström PT, Jonsson MA, Runnerstam M, Silander HC, Ben-Menachem E. Cognition-enhancing effect of vagus nerve stimulation in patients with Alzheimer's disease: A pilot study. *Journal of Clinical Psychiatry*. 2002 Nov 2002;63(11):972-80.
491. Smith DF, Stork BS, Wegener G, Ashkanian M, Jakobsen S, Bender D, et al. [¹¹C]mirtazapine binding in depressed antidepressant nonresponders studied by PET neuroimaging. *Psychopharmacology*. 2009;206(1):133-40.
492. Sobiś J, Jarząb M, Hese RT, Sieroń A, Zyss T, Gorczyca P, et al. Therapeutic efficacy assessment of weak variable magnetic fields with low value of induction in patients with drug-resistant depression. *Journal of Affective Disorders*. 2010;123(1-3):321-6.
493. Solyom L, Solyom C, Ledwidge B. Fluoxetine in panic disorder. *The Canadian Journal of Psychiatry / La Revue canadienne de psychiatrie*. 1991 06;36(5):378-80.
494. Sommer M, Dieterich A, Rütther E, Paulus W, Wiltfang J. Increased transcranial magnetic motor threshold after ECT: a case report. *European Archives of Psychiatry and Clinical Neuroscience*. 2002 2002;252(5):250-2.
495. Sonino N, Navarrini C, Ruini C, Ottolini F, Paoletta A, Fallo F, et al. Persistent psychological distress in patients treated for endocrine disease. *Psychotherapy and Psychosomatics*. 2004 Mar-Apr 2004;73(2):78-83.
496. Sookman D, Pinard G. Integrative cognitive therapy for obsessive-compulsive disorder: a focus on multiple schemas. *Cognitive and Behavioral Practice*. 1999 Fall 1999;6(4):351-62.
497. Sovner R. Amphetamine and tranylcypromine in treatment-resistant depression. *Biological Psychiatry*. 1990 12;28(11):1011-2.
498. Speer AM, Benson BE, Kimbrell TK, Wassermann EM, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on mood in depressed patients: Relationship to baseline cerebral activity on PET. *Journal of Affective Disorders*. 2009;115(3):386-94.
499. Speer AM, Kimbrell TA, Wassermann EM, Repella JD, Willis MW, Herscovitch P, et al. Opposite effects of high and low frequency rTMS on regional brain activity in depressed patients. *Biological Psychiatry*. 2000 Dec 2000;48(12):1133-41.
500. Sperling W, Reulbach U, C M, Kornhuber J, Bleich S. Vagus nerve stimulation in a patient with Gilles de la Tourette syndrome and major depression. *Pharmacopsychiatry*. 2008 May 2008;41(3):117-8.

501. Sperry L. Effective couples therapy and psych 101: you can't have one without the other. *American Journal of Family Therapy*. 2004 Jul-Sep 2004;32(4):325-35.
502. Spirito A, Abebe KZ, Iyengar S, Brent D, Vitiello B, Clarke G, et al. Sources of site differences in the efficacy of a multisite clinical trial: The treatment of SSRI-resistant depression in adolescents. *Journal of Consulting and Clinical Psychology*. 2009 Jun 2009;77(3):439-50.
503. Staller JA. Chronic complex depression. *Psychiatric Services*. 2003 Jun 2003;54(6):771.
504. Stålsett G, Engedal LG, Austad A. The persecuting God and the crucified self: The case of Olav and the transformation of his pathological self-image. *Pragmatic Case Studies in Psychotherapy*. 2010;6(2):49-133.
505. Stamm TJ, Adli M, Kircheiner J, Smolka MN, Kaiser R, Tremblay PB, et al. Serotonin transporter gene and response to lithium augmentation in depression. *Psychiatric Genetics*. 2008 04;18(2):92-7.
506. Steele JD, Glabus MF, Shajahan PM, Ebmeier KP. Increased cortical inhibition in depression: a prolonged silent period with transcranial magnetic stimulation (TMS). *Psychological Medicine*. 2000 May 2000;30(3):565-70.
507. Stefan K, Wycislo M, Gentner R, Schramm A, Naumann M, Reiners K, et al. Temporary occlusion of associative motor cortical plasticity by prior dynamic motor training. *Cerebral Cortex*. 2006 Mar 2006;16(3):376-85.
508. Stewart JW, McGrath PJ, Deliyannides DA, Quitkin FM. Does dual antidepressant therapy as initial treatment hasten and increase remission from depression? *Journal of Psychiatric Practice*. 2009;15(5):337-45.
509. Suarez RO, Golby A, Whalen S, Sato S, Theodore WH, Kufta CV, et al. Contributions to singing ability by the posterior portion of the superior temporal gyrus of the non-language-dominant hemisphere: First evidence from subdural cortical stimulation, WADA testing, and fMRI. *Cortex: A Journal Devoted to the Study of the Nervous System and Behavior*. 2010;46(3):343-53.
510. Subramanian P, Burhan A. Worsening of "passivity" symptoms with low-frequency bilateral temporo-parietal repetitive transcranial magnetic stimulation used to treat refractory auditory hallucinations: A case report. *Schizophrenia Research*. 2010;116(2-3):291-2.
511. Sussman N. Anxiolytic antidepressant augmentation. *Journal of Clinical Psychiatry*. 1998;59(5):42-50.
512. Sutherland EM, Oliver JE, Knight DR. E E G, memory and confusion in dominant, non-dominant and bi-temporal E C T. *British Journal of Psychiatry*. 1969;115(526):1059-64.
513. Svensson P, Miles TS, McKay D, Ridding MC. Suppression of motor evoked potentials in a hand muscle following prolonged painful stimulation. *European Journal of Pain*. 2003 Feb 2003;7(1):55-62.
514. Taylor FB, Prather MR. The efficacy of nefazodone augmentation for treatment-resistant depression with anxiety symptoms or anxiety disorder. *Depression and Anxiety*. 2003;18(2):83-8.
515. Teodor Hese R, Jedrzejewska B. Multiple EEG examinations in patients with recurrent, refractory major depression and bipolar depression after course of UECT. *Archives of Psychiatry and Psychotherapy*. 2000 Sep 2000;2(3):17-24.
516. Terney D, Chaieb L, Moliadze V, Antal A, Paulus W. Increasing human brain excitability by transcranial high-frequency random noise stimulation. *Journal of Neuroscience*. 2008 Dec 2008;28(52):14147-55.
517. Thase ME, Feighner JP, Lydiard RB. Citalopram treatment of fluoxetine nonresponders. *Journal of Clinical Psychiatry*. 2001 09;62(9):683-7.
518. Thase ME, Reynolds CF, Frank E, Simons AD, et al. Response to cognitive-behavioral therapy in chronic depression. *Journal of Psychotherapy Practice & Research*. 1994 Sum 1994;3(3):204-14.

519. Thirthalli J, Kumar CN, Bangalore RP, Gangadhar BN. Speed of response to threshold and suprathreshold bilateral ECT in depression, mania and schizophrenia. *Journal of Affective Disorders*. 2009;117(1-2):104-7.
520. Tkachuk GA. Controlled trial of a multicomponent cognitive-behavioral group treatment for irritable bowel syndrome. *Dissertation Abstracts International: Section B: The Sciences and Engineering*. 2002 Apr 2002;62(10):4807.
521. Tracy DK, O'Daly O, Joyce DW, Michalopoulou PG, Basit BB, Dhillon G, et al. An evoked auditory response fMRI study of the effects of rTMS on putative AVH pathways in healthy volunteers. *Neuropsychologia*. 2010;48(1):270-7.
522. Triggs WJ, McCoy KJM, Greer R, Rossi F, Bowers D, Kortenkamp S, et al. Effects of left frontal transcranial magnetic stimulation on depressed mood, cognition, and corticomotor threshold. *Biological Psychiatry*. 1999 Jun 1999;45(11):1440-6.
523. Tsai H-C, Chen S-Y, Tsai S-T, Hung H-Y, Chang C-H. Hypomania following bilateral ventral capsule stimulation in a patient with refractory obsessive-compulsive disorder. *Biological Psychiatry*. 2010;68(2):e7-e8.
524. Turner RM. The Cognitive-Behavior Therapy Case Conference. *Cognitive and Behavioral Practice*. 1998;5(2):297-307.
525. Tutty S, Ludman EJ, Simon G. Feasibility and acceptability of a telephone psychotherapy program for depressed adults treated in primary care. *General Hospital Psychiatry*. 2005 Nov-Dec 2005;27(6):400-10.
526. Ueda S, Koyama K, Okubo Y. Marked improvement of psychotic symptoms after electroconvulsive therapy in Parkinson disease. *The Journal of ECT*. 2010;26(2):111-5.
527. Valevski A, Pickholtz E, Roz N, Weizman A, Rehavi M. Lack of modulatory effect of short-term repeated electroconvulsive therapy on platelet vesicular monoamine transporter 2 (VMAT2) in depressed patients. *Journal of Neural Transmission*. 2010;117(7):881-5.
528. Valdeoriola F, Regidor I, Mínguez-Castellanos A, Lezcano E, García-Ruiz P, Rojo A, et al. Efficacy and safety of pallidal stimulation in primary dystonia: Results of the Spanish multicentric study. *Journal of Neurology, Neurosurgery & Psychiatry*. 2010;81(1):65-9.
529. van Amelsvoort T. Serious hypertensive reaction after switching from clomipramine to moclobemide. *Irish Journal of Psychological Medicine*. 1998 Jun 1998;15(2):77-8.
530. Van Ameringen M, Mancini C, Patterson B, Bennett M. Topiramate augmentation in treatment-resistant obsessive-compulsive disorder: A retrospective, open-label case series. *Depression and Anxiety*. 2006;23(1):1-5.
531. van der Wurff FB, Stek ML, Hoogendijk WJG, Beekman ATF. Discrepancy Between Opinion and Attitude on the Practice of ECT by Psychiatrists Specializing in Old Age in the Netherlands. *The Journal of ECT*. 2004;20(1):37-41.
532. van Honk J, Schutter DJLG, Putman P, de Haan EHF, d'Alfonso AAL. Reductions in phenomenological, physiological and attentional indices of depressive mood after 2 Hz rTMS over the right parietal cortex in healthy human subjects. *Psychiatry Research*. 2003 Aug 2003;120(1):95-101.
533. Vedel E, Emmelkamp PMG. Behavioral couple therapy in the treatment of a female alcohol-dependent patient with comorbid depression, anxiety, and personality disorders. *Clinical Case Studies*. 2004 Jul 2004;3(3):187-205.
534. Vedeniapin A, Cheng L, George MS. Feasibility of simultaneous cognitive behavioral therapy and left prefrontal rTMS for treatment resistant depression. *Brain Stimulation*. 2010;3(4):207-10.
535. Velasco M, Velasco F, Jiménez F, Carrillo-Ruiz JD, Velasco AL, SalIn-Pascual R. Electroconvulsive and behavioral responses elicited by acute electrical stimulation of inferior thalamic peduncle and nucleus reticularis thalami in a patient with major depression disorder. *Clinical Neurophysiology*. 2006 Feb 2006;117(2):320-7.

536. Vercammen A, Knegtering H, Bruggeman R, Westenbroek HM, Jenner JA, Slooff CJ, et al. Effects of bilateral repetitive transcranial magnetic stimulation on treatment resistant auditory-verbal hallucinations in schizophrenia: A randomized controlled trial. *Schizophrenia Research*. 2009;114(1-3):172-9.
537. Vercammen A, Knegtering H, Liemburg EJ, den Boer JA, Aleman A. Functional connectivity of the temporo-parietal region in schizophrenia: Effects of rTMS treatment of auditory hallucinations. *Journal of Psychiatric Research*. 2010;44(11):725-31.
538. Verhoeven W, Tuinier S, Egger J, van Erp F, Tuerlings J. Avolition in a patient with hypogonadism. *European Journal of Psychiatry*. 2008 10;22(4):195-9.
539. Vinar O, Vinarova E. Tianeptine helps depressed patients resistant to serotonin function enhancing drugs. *Homeostasis in Health and Disease*. 1997 09;38(4):170-2.
540. Vulink NCC, Denys D, Fluitman SBAHA, Meinardi JCM, Westenberg HGM. Quetiapine augments the effect of citalopram in non-refractory obsessive-compulsive disorder: A randomized, double-blind, placebo-controlled study of 76 patients. *Journal of Clinical Psychiatry*. 2009;70(7):1001-8.
541. Wachtel LE, Griffin M, Reti IM. Electroconvulsive therapy in a man with autism experiencing severe depression, catatonia, and self-injury. *The Journal of ECT*. 2010;26(1):70-3.
542. Wada T, Kanno M, Aoshima T, Otani K. Dose-dependent augmentation effect of bromocriptine in a case with refractory depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. 2001 02;25(2):457-62.
543. Wagner KD. Major depression in children and adolescents. *Psychiatric Annals*. 2003 Apr 2003;33(4):266-70.
544. Walter G, Tormos JM, Israel JA, Pascual-Leone A. Transcranial magnetic stimulation in young persons: A review of known cases. *Journal of Child and Adolescent Psychopharmacology*. 2001 Spr 2001;11(1):69-75.
545. Wang H, Chen X, Lin Z, Shao Z, Sun B, Shen H, et al. Long-term effect of vagus nerve stimulation on interictal epileptiform discharges in refractory epilepsy. *Journal of the Neurological Sciences*. 2009;284(1-2):96-102.
546. Warnell RL, Elahi N. Introduction of vagus nerve stimulation into a maintenance electroconvulsive therapy regimen: A case study and cost analysis. *Journal of ECT*. 2007 Jun 2007;23(2):114-9.
547. Wasserman EM, Greenberg BD, Nguyen MB, Murphy DL. Motor cortex excitability correlates with an anxiety-related personality trait. *Biological Psychiatry*. 2001 Sep 2001;50(5):377-82.
548. Watts BV, Groft A. Retrospective evaluation of the dexamethasone suppression test as a predictor of response to electroconvulsive therapy in patients with comorbid major depressive disorder and posttraumatic stress disorder. *The Journal of ECT*. 2010;26(3):213-7.
549. Weise D, Schramm A, Stefan K, Wolters A, Reiners K, Naumann M, et al. The two sides of associative plasticity in writer's cramp. *Brain: A Journal of Neurology*. 2006 Oct 2006;129(10):2709-21.
550. Westra HA. Managing resistance in cognitive behavioural therapy: the application of motivational interviewing in mixed anxiety and depression. *Cognitive Behaviour Therapy*. 2004;33(4):161-75.
551. Wilz G, Barskova T. Evaluation of a cognitive behavioral group intervention program for spouses of stroke patients. *Behaviour Research and Therapy*. 2007 Oct 2007;45(10):2508-17.
552. Wolters A, Sandbrink F, Schlottmann A, Kunesch E, Stefan K, Cohen LG, et al. A temporally asymmetric hebbian rule governing plasticity in the human motor cortex. *Journal of Neurophysiology*. 2003 May 2003;89(5):2339-45.
553. Worthington JJ, III, Kinrys G, Wygant LE, Pollack MH. Aripiprazole as an augmentor of selective serotonin reuptake inhibitors in depression and anxiety disorder patients. *International Clinical Psychopharmacology*. 2005 01;20(1):9-11.

554. Wright JH. A 25-year-old man with chronic severe depression. *Psychiatric Annals*. 2003 Sep 2003;33(9):552-4.
555. Wright JH. Cognitive behavior therapy for chronic depression: combined treatment may succeed when pharmacologic monotherapy fails. *Psychiatric Annals*. 2003 Dec 2003;33(12):777-84.
556. Wu W-H, Huo S-J, Chih-Ya C, Chen-Jee H, Tsai S-J. Association study of the 5-HT(6) receptor polymorphism (C267T) and symptomatology and antidepressant response in major depressive disorders. *Neuropsychobiology*. 2001 11;44(4):172-5.
557. Yatham LN, Liddle PF, Lam RW, Zis AP, Stoessel AJ, Sossi V, et al. Effect of electroconvulsive therapy on brain 5-HT₂ receptors in major depression. *British Journal of Psychiatry*. 2010;196(6):474-9.
558. Yeh Y-W, Chen C-H, Kuo S-C, Wang S-C, Chen C-K, Feng H-M. High-dose duloxetine for treatment-resistant obsessive-compulsive disorder: A case report with sustained full remission. *Clinical neuropharmacology*. 2009;32(3):174-6.
559. Yoshida K, Sugawara Y, Higuchi H. Dramatic Remission of Treatment-resistant Depression after the Cessation of Tricyclic Antidepressants: A Case Report. *Pharmacopsychiatry*. 2006 05;39(3):114-.
560. Yoshimi A, Togo T, Sugiyama N, Uehara K, Otsuka T, Karashima A, et al. Treatment of refractory tardive dyskinesia with donepezil in an elderly patient with depression. *Psychogeriatrics*. 2008;8(4):196-8.
561. Zahodne LB, Okun MS, Foote KD, Fernandez HH, Rodriguez RL, Kirsch-Darrow L, et al. Cognitive declines one year after unilateral deep brain stimulation surgery in Parkinson's disease: A controlled study using reliable change. *The Clinical Neuropsychologist*. 2009;23(3):385-405.
562. Zarate CA, Jr., Payne JL, Quiroz J, Sporn J, Denicoff KK, Luckenbaugh D, et al. An Open-Label Trial of Riluzole in Patients With Treatment-Resistant Major Depression. *The American Journal of Psychiatry*. 2004 01;161(1):171-4.
563. Zhang T-J, Wu Q-Z, Huang X-Q, Sun X-L, Zou K, Lui S, et al. Magnetization transfer imaging reveals the brain deficit in patients with treatment-refractory depression. *Journal of Affective Disorders*. 2009;117(3):157-61.
564. Zhang X, Zhang Z, Sha W, Xie C, Xi G, Zhou H, et al. Electroconvulsive therapy increases glial cell-line derived neurotrophic factor (GDNF) serum levels in patients with drug-resistant depression. *Psychiatry Research*. 2009;170(2-3):273-5.
565. Zheng XM. Regional cerebral blood flow changes in drug-resistant depressed patients following treatment with transcranial magnetic stimulation: A statistical parametric mapping analysis. *Psychiatry Research: Neuroimaging*. 2000 Dec 2000;100(2):75-80.
566. Ziemann U, Iliac TV, Pauli C, Meintzschel F, Ruge D. Learning modifies subsequent induction of long-term potentiation-like and long-term depression-like plasticity in human motor cortex. *Journal of Neuroscience*. 2004 Feb 2004;24(7):1666-72.
567. Zisook S, Chentsova-Dutton YE, Smith-Vaniz A, Kline NA, Ellenor GL, Kodsí AB, et al. Nefazodone in patients with treatment-refractory posttraumatic stress disorder. *Journal of Clinical Psychiatry*. 2000 03;61(3):203-8.
568. Zöger S, Erlandsson S, Svedlund J, Holgers K-M. Benefits from group psychotherapy in the treatment of severe refractory tinnitus. *Audiological Medicine*. 2008 2008;6(1):62-72.
569. Zwanzger P, Baghai TC, Padberg F, Ella R, Minov C, Mikhael P, et al. The combined dexamethasone-CRH test before and after repetitive transcranial magnetic stimulation (rTMS) in major depression. *Psychoneuroendocrinology*. 2003 Apr 2003;28(3):376-85.
570. Zwanzger P, Ella R, Keck ME, Rupprecht R, Padberg F. Occurrence of delusions during repetitive transcranial magnetic stimulation (rTMS) in major depression. *Biological Psychiatry*. 2002 Apr 2002;51(7):602-3.

571. Zwanzger P, Eser D, Völkel N, Baghai TC, Möller H-J, Rupprecht R, et al. Effects of repetitive transcranial magnetic stimulation (rTMS) on panic attacks induced by cholecystokinin-tetrapeptide (CCK-4). *International Journal of Neuropsychopharmacology*. 2007 Apr 2007;10(2):285-9.
572. Berman RM, Narasimhan M, Sanacora G, Miano AP, Hoffman RE, Hu XS, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry*. 2000 Feb 2000;47(4):332-7.
573. Boutros NN, Gueorguieva R, Hoffman RE, Oren DA, Feingold A, Berman RM. Lack of a therapeutic effect of a 2-week sub-threshold transcranial magnetic stimulation course for treatment-resistant depression. *Psychiatry Research*. 2002 Dec 2002;113(3):245-54.
574. Fang Y, Yuan C, Xu Y, Chen J, Wu Z, Cao L, et al. Comparisons of the efficacy and tolerability of extended-release venlafaxine, mirtazapine, and paroxetine in treatment-resistant depression: A double-blind, randomized pilot study in a Chinese population. *Journal of Clinical Psychopharmacology*. US: Lippincott Williams & Wilkins 2010:357-64.
575. Garcia-Toro M, Mayol A, Arnillas H, Capllonch I, Ibarra O, Crespi M, et al. Modest adjunctive benefit with transcranial magnetic stimulation in medication-resistant depression. *Journal of Affective Disorders*. 2001 May 2001;64(2):271-5.
576. Knapp M, Romeo R, Mogg A, Eranti S, Pluck G, Purvis R, et al. Cost-effectiveness of transcranial magnetic stimulation vs electroconvulsive therapy for severe depression: A multi-centre randomised controlled trial. *Journal of Affective Disorders* 2008:273-85.
577. Kocsis JH, Gelenberg AJ, Rothbaum BO, Klein DN, Trivedi MH, Manber R, et al. Cognitive behavioral analysis system of psychotherapy and brief supportive psychotherapy for augmentation of antidepressant nonresponse in chronic depression: The REVAMP trial. *Archives of General Psychiatry*. US: American Medical Assn 2009:1178-88.
578. Manes F, Jorge R, Morcuende M, Yamada T, Paradiso S, Robinson RG. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *International Psychogeriatrics*. 2001 Jun 2001;13(2):225-31.
579. Möller AL, Hjaltason Ó, Ívarsson Ó, Stefánsson SB. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P-sub-3-sub-0-sub-0 event-related potential. *Nordic Journal of Psychiatry*. 2006 2006;60(4):282-5.
580. Moore RG, Blackburn I-M. Cognitive therapy in the treatment of non-responders to antidepressant medication: A controlled pilot study. *Behavioural and Cognitive Psychotherapy*. 1997 1997;25(3):251-9.
581. Moser DJ, Jorge RE, Manes F, Paradiso S, Benjamin ML, Robinson RG. Improved executive functioning following repetitive transcranial magnetic stimulation. *Neurology* 2002:1288-90.
582. Nierenberg AA, Papakostas GI, Petersen T, Montoya HD, Worthington JJ, Tedlow J, et al. Lithium augmentation of nortriptyline for subjects resistant to multiple antidepressants. *Journal of Clinical Psychopharmacology*. US: Lippincott Williams & Wilkins 2003:92-5.
583. Su T-P, Huang C-C, Wei IH. Add-On rTMS for medication-resistant depression: a randomized, double-blind, sham-controlled trial in Chinese patients. *Journal of Clinical Psychiatry*. 2005 Jul 2005;66(7):930-7.
584. Wiles NJ, Hollinghurst S, Mason V, Musa M, Burt V, Hyde J, et al. A randomized controlled trial of cognitive behavioural therapy as an adjunct to pharmacotherapy in primary care based patients with treatment resistant depression: A pilot study. *Behavioural and Cognitive Psychotherapy*. 2008 Jan 2008;36(1):21-33.
585. Zheng H, Zhang L, Li L, Liu P, Gao J, Liu X, et al. High-frequency rTMS treatment increases left prefrontal myo-inositol in young patients with treatment-resistant depression. *Progress in Neuro-Psychopharmacology & Biological Psychiatry*. Netherlands: Elsevier Science 2010:1189-95.

586. Kauffmann CD, Cheema MA, Miller BE. Slow right prefrontal transcranial magnetic stimulation as a treatment for medication-resistant depression: a double-blind, placebo-controlled study. *Depression and Anxiety*. 2004;19(1):59-62.
587. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson SM, McDonald WM, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation*. Netherlands: Elsevier Science 2010:187-99.
588. Rush AJ, Marangell LB, Sackeim HA, George MS, Brannan SK, Davis SM, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry*. 2005 Sep 2005;58(5):347-54.
589. Thase ME, Corya SA, Osuntokun O, Case M, Henley DB, Sanger TM, et al. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, and fluoxetine in treatment-resistant major depressive disorder. *Journal of Clinical Psychiatry*. US: Physicians Postgraduate Press 2007:224-36.
6. Easing the burden of treatment-resistant depression. *J Clin Psychiatry*. 2009 Feb;70(2):273-80.
7. Options for treatment-resistant depression. Why electroconvulsive therapy may be the best alternative to medication. *Harv Ment Health Lett*. 2009 Jan;25(7):1-3.
8. Transcranial magnetic stimulation. Research helps clarify who is likely to benefit from this treatment. *Harv Ment Health Lett*. 2010 Sep;27(3):6.
9. Abbass AA. Intensiveshort-term dynamic psychotherapy of treatment-resistant depression: a pilot study. *Depress Anxiety*. 2006;23(7):449-52.
10. Ables AZ, Baughman OL, 3rd. Antidepressants: update on new agents and indications. *Am Fam Physician*. 2003 Feb 1;67(3):547-54.
11. Abou-Saleh MT, Anderson DN, Collins J, Hughes K, Cattell RJ, Hamon CG, et al. The role of pterins in depression and the effects of antidepressive therapy. *Biol Psychiatry*. 1995 Oct 1;38(7):458-63.
12. Abraham G, Milev R, Stuart Lawson J. T3 augmentation of SSRI resistant depression. *J Affect Disord*. 2006 Apr;91(2-3):211-5.
13. Abrams R. Is unilateral electroconvulsive therapy really the treatment of choice in endogenous depression? *Ann N Y Acad Sci*. 1986;462:50-5.

PubMed = 1,384 articles (excluding duplicates)

1. Recognize the subtleties of depression in primary care. *Dis Manag Advis*. 2002 Feb;8(2):28-32, 17.
2. Vagus nerve stimulation for treatment-resistance depression. *Technol Eval Cent Asses Program Exec Summ*. 2005 Aug;20(8):1-2.
3. Drug treatments for bipolar disorder: 1-- Acute manic or depressive episodes. *Drug Ther Bull*. 2005 Apr;43(4):28-32.
4. Magnetic stimulation as therapy. Unlocking depression, chronic pain and more. *Mayo Clin Health Lett*. 2009 Dec;27(12):1-3.
5. Transcranial magnetic stimulation for depression. *Technol Eval Cent Asses Program Exec Summ*. 2009 Oct;24(5):1-3.
14. Abrams R, Swartz CM, Vedak C. Antidepressant effects of right versus left unilateral ECT and the lateralization theory of ECT action. *Am J Psychiatry*. 1989 Sep;146(9):1190-2.
15. Abrams R, Swartz CM, Vedak C. Antidepressant effects of high-dose right unilateral electroconvulsive therapy. *Arch Gen Psychiatry*. 1991 Aug;48(8):746-8.
16. Abrams R, Volavka J, Schrifft M. Brief pulse ECT in melancholia. EEG and clinical effects. *J Nerv Ment Dis*. 1992 Jan;180(1):55-7.
17. Ackerman DL, Unutzer J, Greenland S, Gitlin M. Inpatient treatment of depression and associated hospital charges. *Pharmacoepidemiol Drug Saf*. 2002 Apr-May;11(3):219-27.

18. Adlersberg S, Toren P, Mester R, Rehavi M, Skolnick P, Weizman A. Verapamil is not an antidepressant in patients resistant to tricyclic antidepressants. *Clin Neuropharmacol.* 1994 Jun;17(3):294-7.
19. Adli M, Baethge C, Heinz A, Langlitz N, Bauer M. Is dose escalation of antidepressants a rational strategy after a medium-dose treatment has failed? A systematic review. *Eur Arch Psychiatry Clin Neurosci.* 2005 Dec;255(6):387-400.
20. Adli M, Berghofer A, Linden M, Helmchen H, Muller-Oerlinghausen B, Mackert A, et al. Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a 2-year observational algorithm study. *J Clin Psychiatry.* 2002 Sep;63(9):782-90.
21. Adli M, Hollinde DL, Stamm T, Wiethoff K, Tsahuridu M, Kirchheiner J, et al. Response to lithium augmentation in depression is associated with the glycogen synthase kinase 3-beta -50T/C single nucleotide polymorphism. *Biol Psychiatry.* 2007 Dec 1;62(11):1295-302.
22. Adli M, Pilhatsch M, Bauer M, Koberle U, Ricken R, Janssen G, et al. Safety of high-intensity treatment with the irreversible monoamine oxidase inhibitor tranylcypromine in patients with treatment-resistant depression. *Pharmacopsychiatry.* 2008 Nov;41(6):252-7.
23. Adli M, Rush AJ, Moller HJ, Bauer M. Algorithms for optimizing the treatment of depression: making the right decision at the right time. *Pharmacopsychiatry.* 2003 Nov;36 Suppl 3:S222-9.
24. Agelink MW, Andrich J, Postert T, Wurzinger U, Zeit T, Klotz P, et al. Relation between electroconvulsive therapy, cognitive side effects, neuron specific enolase, and protein S-100. *J Neurol Neurosurg Psychiatry.* 2001 Sep;71(3):394-6.
25. Agius M, Gardner J, Liu K, Zaman R. An audit to compare discharge rates between antidepressant monotherapies prescribed for pure unipolar depression versus depression in the presence of other indications. *Psychiatr Danub.* 2010 Jun;22(2):346-9.
26. Aguera LF, Rojo JE, Ros S, de la Gandara J, de Pedro JM. Antidepressant combinations: epidemiological considerations. *Acta Psychiatr Scand Suppl.* 2005(428):7-10, 36.
27. Ahdab R, Ayache SS, Brugieres P, Goujon C, Lefaucheur JP. Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiol Clin.* 2010 Mar;40(1):27-36.
28. Ahmed SH, Zaheeruddin. Early experience with fluoxetine. *J Pak Med Assoc.* 1991 Nov;41(11):275-7.
29. Akiskal HS. A proposed clinical approach to chronic and "resistant" depressions: evaluation and treatment. *J Clin Psychiatry.* 1985 Oct;46(10 Pt 2):32-7.
30. Akiskal HS. Approach to chronic and treatment-resistant depressions. *Adv Biochem Psychopharmacol.* 1985;40:159-63.
31. Alao AO, Malhotra K, Pies R, Dewan MJ. Pharmacological strategies in treatment-resistant depression. *West Afr J Med.* 2003 Sep;22(3):211-8.
32. Albers LJ, Reist C, Helme D, Vu R, Tang SW. Paroxetine shifts imipramine metabolism. *Psychiatry Res.* 1996 Jan 31;59(3):189-96.
33. Alexopoulos GS, Canuso CM, Gharabawi GM, Bossie CA, Greenspan A, Turkoz I, et al. Placebo-controlled study of relapse prevention with risperidone augmentation in older patients with resistant depression. *Am J Geriatr Psychiatry.* 2008 Jan;16(1):21-30.
34. Alpert JE, Papakostas G, Mischoulon D, Worthington JJ, 3rd, Petersen T, Mahal Y, et al. S-adenosyl-L-methionine (SAME) as an adjunct for resistant major depressive disorder: an open trial following partial or nonresponse to selective serotonin reuptake inhibitors or venlafaxine. *J Clin Psychopharmacol.* 2004 Dec;24(6):661-4.
35. Altamura AC, Dell'Osso B, Buoli M, Bosi M, Mundo E. Short-term intravenous citalopram augmentation in partial/nonresponders with major depression: a randomized placebo-controlled study. *Int Clin Psychopharmacol.* 2008 Jul;23(4):198-202.

36. Altamura AC, Dell'Osso B, Buoli M, Zanoni S, Mundo E. Intravenous augmentative citalopram versus clomipramine in partial/nonresponder depressed patients: a short-term, low dose, randomized, placebo-controlled study. *J Clin Psychopharmacol.* 2008 Aug;28(4):406-10.
37. Amiaz R, Stein O, Schreiber S, Danon PN, Dolberg OT, Grunhaus L. Magnetic and seizure thresholds before and after six electroconvulsive treatments. *J Ect.* 2001 Sep;17(3):195-7.
38. Amital D, Fostick L, Silberman A, Beckman M, Spivak B. Serious life events among resistant and non-resistant MDD patients. *J Affect Disord.* 2008 Oct;110(3):260-4.
39. Amsterdam JD, Berwisch N. Treatment of refractory depression with combination reserpine and tricyclic antidepressant therapy. *J Clin Psychopharmacol.* 1987 Aug;7(4):238-42.
40. Amsterdam JD, Berwisch NJ. High dose tranylecypromine therapy for refractory depression. *Pharmacopsychiatry.* 1989 Jan;22(1):21-5.
41. Amsterdam JD, Garcia-Espana F, Rosenzweig M. Clomipramine augmentation in treatment-resistant depression. *Depress Anxiety.* 1997;5(2):84-90.
42. Amsterdam JD, Hornig-Rohan M. Treatment algorithms in treatment-resistant depression. *Psychiatr Clin North Am.* 1996 Jun;19(2):371-86.
43. Amsterdam JD, Maislin G, Potter L. Fluoxetine efficacy in treatment resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 1994 Mar;18(2):243-61.
44. Amsterdam JD, Shults J. MAOI efficacy and safety in advanced stage treatment-resistant depression--a retrospective study. *J Affect Disord.* 2005 Dec;89(1-3):183-8.
45. Ananth J. Treatment-resistant depression. *Psychother Psychosom.* 1998;67(2):61-70.
46. Anderson DN, Wilkinson AM, Abou-Saleh MT, Blair JA. Recovery from depression after electroconvulsive therapy is accompanied by evidence of increased tetrahydrobiopterin-dependent hydroxylation. *Acta Psychiatr Scand.* 1994 Jul;90(1):10-3.
47. Anderson IM, Delvai NA, Ashim B, Ashim S, Lewin C, Singh V, et al. Adjunctive fast repetitive transcranial magnetic stimulation in depression. *Br J Psychiatry.* 2007 Jun;190:533-4.
48. Andrews JM, Nemeroff CB. Contemporary management of depression. *Am J Med.* 1994 Dec 19;97(6A):24S-32S.
49. Andrews JM, Ninan PT, Nemeroff CB. Venlafaxine: a novel antidepressant that has a dual mechanism of action. *Depression.* 1996;4(2):48-56.
50. Antai-Otong D. The art of prescribing. Monotherapy antidepressant: a thing of the past? Implications for the treatment of major depressive disorder. *Perspect Psychiatr Care.* 2007 Jul;43(3):142-5.
51. Antonuccio DO, Akins WT, Chatham PM, Monagin JA, Tearman BH, Ziegler BL. An exploratory study: the psychoeducational group treatment of drug-refractory unipolar depression. *J Behav Ther Exp Psychiatry.* 1984 Dec;15(4):309-13.
52. Anttila S, Huuhka K, Huuhka M, Rontu R, Hurme M, Leinonen E, et al. Interaction between 5-HT1A and BDNF genotypes increases the risk of treatment-resistant depression. *J Neural Transm.* 2007;114(8):1065-8.
53. Antunes PB, Fleck MP. Clinical outcomes and quality of life in patients submitted to electroconvulsive therapy. *J ECT.* 2009 Sep;25(3):182-5.
54. Aoyama Y, Hanaoka N, Kameyama M, Suda M, Sato T, Song M, et al. Stimulus intensity dependence of cerebral blood volume changes in left frontal lobe by low-frequency rTMS to right frontal lobe: A near-infrared spectroscopy study. *Neurosci Res.* 2009 Jan;63(1):47-51.
55. Appelberg BG, Syvalahti EK, Koskinen TE, Mehtonen OP, Muhonen TT, Naukkarinen HH. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-blind, placebo wash-in study. *J Clin Psychiatry.* 2001 Jun;62(6):448-52.

56. Arean PA, Alvidrez J. Treating depressive disorders: who responds, who does not respond, and who do we need to study? *J Fam Pract.* 2001 Jun;50(6):E2.
57. Armitage R, Husain M, Hoffmann R, Rush AJ. The effects of vagus nerve stimulation on sleep EEG in depression: a preliminary report. *J Psychosom Res.* 2003 May;54(5):475-82.
58. Aronson R, Offman HJ, Joffe RT, Naylor CD. Triiodothyronine augmentation in the treatment of refractory depression. A meta-analysis. *Arch Gen Psychiatry.* 1996 Sep;53(9):842-8.
59. Aronson TA, Shukla S, Hoff A, Cook B. Proposed delusional depression subtypes: preliminary evidence from a retrospective study of phenomenology and treatment course. *J Affect Disord.* 1988 Jan-Feb;14(1):69-74.
60. Artigas F, Romero L, de Montigny C, Blier P. Acceleration of the effect of selected antidepressant drugs in major depression by 5-HT_{1A} antagonists. *Trends Neurosci.* 1996 Sep;19(9):378-83.
61. Ashton AK. Depressive relapse after vagal nerve stimulator explantation. *Am J Psychiatry.* 2010 Jun;167(6):719-20.
62. Asnis GM, Halbreich U, Nathan RS, Ostrow L, Novacenko H, Endicott J, et al. The dexamethasone suppression test in depressive illness: clinical correlates. *Psychoneuroendocrinology.* 1982;7(4):295-301.
63. Austin MP, Souza FG, Goodwin GM. Lithium augmentation in antidepressant-resistant patients. A quantitative analysis. *Br J Psychiatry.* 1991 Oct;159:510-4.
64. Avery DH, Claypoole K, Robinson L, Neumaier JF, Dunner DL, Scheele L, et al. Repetitive transcranial magnetic stimulation in the treatment of medication-resistant depression: preliminary data. *J Nerv Ment Dis.* 1999 Feb;187(2):114-7.
65. Avery DH, Holtzheimer PE, 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. A controlled study of repetitive transcranial magnetic stimulation in medication-resistant major depression. *Biol Psychiatry.* 2006 Jan 15;59(2):187-94.
66. Avery DH, Holtzheimer PE, 3rd, Fawaz W, Russo J, Neumaier J, Dunner DL, et al. Transcranial magnetic stimulation reduces pain in patients with major depression: a sham-controlled study. *J Nerv Ment Dis.* 2007 May;195(5):378-81.
67. Avery DH, Isenberg KE, Sampson SM, Janicak PG, Lisanby SH, Maixner DF, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry.* 2008 Mar;69(3):441-51.
68. Avramov MN, Husain MM, White PF. The comparative effects of methohexital, propofol, and etomidate for electroconvulsive therapy. *Anesth Analg.* 1995;81(3):596-602.
69. Awata S, Konno M, Kawashima R, Suzuki K, Sato T, Matsuoka H, et al. Changes in regional cerebral blood flow abnormalities in late-life depression following response to electroconvulsive therapy. *Psychiatry Clin Neurosci.* 2002 Feb;56(1):31-40.
70. Aymard N, Viala A, Baldacci C, Smaghe PO, Vacheron MN, Caroli F. Pharmacoclinical strategy in neuroleptic resistant schizophrenic patients treated by clozapine: clinical evolution, concentration of plasma and red blood cell clozapine and desmethylclozapine, whole blood serotonin and tryptophan. *Prog Neuropsychopharmacol Biol Psychiatry.* 1999 Jan;23(1):25-41.
71. Azuma H, Fujita A, Sato K, Arahata K, Otsuki K, Hori M, et al. Postictal cardiovascular response predicts therapeutic efficacy of electroconvulsive therapy for depression. *Psychiatry Clin Neurosci.* 2007 Jun;61(3):290-4.
72. Babigian HM, Guttmacher LB. Epidemiologic considerations in electroconvulsive therapy. *Arch Gen Psychiatry.* 1984 Mar;41(3):246-53.
73. Bader CD, Dunner DL. Antidepressant-induced hypomania in treatment-resistant depression. *J Psychiatr Pract.* 2007 Jul;13(4):233-7.

74. Baeken C, De Raedt R, Van Hove C, Clerinx P, De Mey J, Bossuyt A. HF-rTMS treatment in medication-resistant melancholic depression: results from 18FDG-PET brain imaging. *CNS Spectr*. 2009 Aug;14(8):439-48.
75. Baetz M, Bowen RC. Efficacy of divalproex sodium in patients with panic disorder and mood instability who have not responded to conventional therapy. *Can J Psychiatry*. 1998 Feb;43(1):73-7.
76. Baghai TC, Marcuse A, Brosch M, Schule C, Eser D, Nothdurfter C, et al. The influence of concomitant antidepressant medication on safety, tolerability and clinical effectiveness of electroconvulsive therapy. *World J Biol Psychiatry*. 2006;7(2):82-90.
77. Baghai TC, Moller HJ. Electroconvulsive therapy and its different indications. *Dialogues Clin Neurosci*. 2008;10(1):105-17.
78. Bailey KP. Treating treatment-resistant depression. Whether to switch, augment, or combine therapies. *J Psychosoc Nurs Ment Health Serv*. 2003 Jun;41(6):14-20.
79. Bailine SH, Rifkin A, Kayne E, Selzer JA, Vital-Herne J, Blieka M, et al. Comparison of bifrontal and bitemporal ECT for major depression. *Am J Psychiatry*. 2000 Jan;157(1):121-3.
80. Bair MJ, Robinson RL, Katon W, Kroenke K. Depression and pain comorbidity: a literature review. *Arch Intern Med*. 2003 Nov 10;163(20):2433-45.
81. Bajbouj M, Brakemeier EL, Schubert F, Lang UE, Neu P, Schindowski C, et al. Repetitive transcranial magnetic stimulation of the dorsolateral prefrontal cortex and cortical excitability in patients with major depressive disorder. *Exp Neurol*. 2005 Dec;196(2):332-8.
82. Bajbouj M, Gallinat J, Lang UE, Hellen F, Vesper J, Lisanby SH, et al. Motor cortex excitability after vagus nerve stimulation in major depression. *J Clin Psychopharmacol*. 2007 Apr;27(2):156-9.
83. Bajbouj M, Gallinat J, Lang UE, Neu P, Niehaus L. Motorcortical excitability after electroconvulsive therapy in patients with major depressive disorder. *Suppl Clin Neurophysiol*. 2003;56:433-40.
84. Bajbouj M, Lang UE, Niehaus L, Hellen FE, Heuser I, Neu P. Effects of right unilateral electroconvulsive therapy on motor cortical excitability in depressive patients. *J Psychiatr Res*. 2006 Jun;40(4):322-7.
85. Bajbouj M, Lisanby SH, Lang UE, Danker-Hopfe H, Heuser I, Neu P. Evidence for impaired cortical inhibition in patients with unipolar major depression. *Biol Psychiatry*. 2006 Mar 1;59(5):395-400.
86. Bajwa S, BERPpohl F, Rigonatti SP, Pascual-Leone A, Boggio PS, Fregni F. Impaired interhemispheric interactions in patients with major depression. *J Nerv Ment Dis*. 2008 Sep;196(9):671-7.
87. Baldessarini RJ. Current status of antidepressants: clinical pharmacology and therapy. *J Clin Psychiatry*. 1989 Apr;50(4):117-26.
88. Baldwin RC, Simpson S. Treatment resistant depression in the elderly: a review of its conceptualisation, management and relationship to organic brain disease. *J Affect Disord*. 1997 Dec;46(3):163-73.
89. Barbee JG, Conrad EJ, Jamhour NJ. The effectiveness of olanzapine, risperidone, quetiapine, and ziprasidone as augmentation agents in treatment-resistant major depressive disorder. *J Clin Psychiatry*. 2004 Jul;65(7):975-81.
90. Bares M, Brunovsky M, Kopecek M, Stopkova P, Novak T, Kozeny J, et al. Changes in QEEG prefrontal cordance as a predictor of response to antidepressants in patients with treatment resistant depressive disorder: a pilot study. *J Psychiatr Res*. 2007 Apr-Jun;41(3-4):319-25.
91. Bares M, Novak T, Kopecek M, Stopkova P, Sos P. Is combined treatment more effective than switching to monotherapy in patients with resistant depression? A retrospective study. *Neuro Endocrinol Lett*. 2009;30(6):723-8.

92. Barker WA, Scott J, Eccleston D. The Newcastle chronic depression study: results of a treatment regime. *Int Clin Psychopharmacol.* 1987 Jul;2(3):261-72.
93. Battersby M, Ben-Tovim D, Eden J. Electroconvulsive therapy: a study of attitudes and attitude change after seeing an educational video. *Aust N Z J Psychiatry.* 1993 Dec;27(4):613-9.
94. Bauer M, Adli M, Baethge C, Berghofer A, Sasse J, Heinz A, et al. Lithium augmentation therapy in refractory depression: clinical evidence and neurobiological mechanisms. *Can J Psychiatry.* 2003 Aug;48(7):440-8.
95. Bauer M, Adli M, Bschor T, Pilhatsch M, Pfennig A, Sasse J, et al. Lithium's emerging role in the treatment of refractory major depressive episodes: augmentation of antidepressants. *Neuropsychobiology.* 2010;62(1):36-42.
96. Bauer M, Baur H, Berghofer A, Strohle A, Hellweg R, Muller-Oerlinghausen B, et al. Effects of supraphysiological thyroxine administration in healthy controls and patients with depressive disorders. *J Affect Disord.* 2002 Apr;68(2-3):285-94.
97. Bauer M, Beaulieu S, Dunner DL, Lafer B, Kupka R. Rapid cycling bipolar disorder--diagnostic concepts. *Bipolar Disord.* 2008 Feb;10(1 Pt 2):153-62.
98. Bauer M, Dopfmer S. Lithium augmentation in treatment-resistant depression: meta-analysis of placebo-controlled studies. *J Clin Psychopharmacol.* 1999 Oct;19(5):427-34.
99. Bauer M, Forsthoff A, Baethge C, Adli M, Berghofer A, Dopfmer S, et al. Lithium augmentation therapy in refractory depression-update 2002. *Eur Arch Psychiatry Clin Neurosci.* 2003 Jun;253(3):132-9.
100. Bauer M, Pfennig A, Linden M, Smolka MN, Neu P, Adli M. Efficacy of an algorithm-guided treatment compared with treatment as usual: a randomized, controlled study of inpatients with depression. *J Clin Psychopharmacol.* 2009 Aug;29(4):327-33.
101. Bauer M, Tharmanathan P, Volz HP, Moeller HJ, Freemantle N. The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: a meta-analysis. *Eur Arch Psychiatry Clin Neurosci.* 2009 Apr;259(3):172-85.
102. Bauer ME, Papadopoulos A, Poon L, Perks P, Lightman SL, Checkley S, et al. Dexamethasone-induced effects on lymphocyte distribution and expression of adhesion molecules in treatment-resistant depression. *Psychiatry Res.* 2002 Dec 15;113(1-2):1-15.
103. Bauer ME, Papadopoulos A, Poon L, Perks P, Lightman SL, Checkley S, et al. Altered glucocorticoid immunoregulation in treatment resistant depression. *Psychoneuroendocrinology.* 2003 Jan;28(1):49-65.
104. Baumann P, Nil R, Souche A, Montaldi S, Baettig D, Lambert S, et al. A double-blind, placebo-controlled study of citalopram with and without lithium in the treatment of therapy-resistant depressive patients: a clinical, pharmacokinetic, and pharmacogenetic investigation. *J Clin Psychopharmacol.* 1996 Aug;16(4):307-14.
105. Baune BT, Caliskan S, Todder D. Effects of adjunctive antidepressant therapy with quetiapine on clinical outcome, quality of sleep and daytime motor activity in patients with treatment-resistant depression. *Hum Psychopharmacol.* 2007 Jan;22(1):1-9.
106. Bean GJ, Marchese V, Martin BA. Electric stimulus energy and the clinical response to electroconvulsive therapy. *Can J Psychiatry.* 1991 Nov;36(9):637-44.
107. Bearn J, Franey C, Arendt J, Checkley SA. A study of the effects of desipramine treatment alone and in combination with L-triiodothyronine on 6-sulphatoxymelatonin excretion in depressed patients. *Br J Psychiatry.* 1989 Sep;155:341-7.
108. Beasley CM, Jr., Saylor ME, Cunningham GE, Weiss AM, Masica DN. Fluoxetine in tricyclic refractory major depressive disorder. *J Affect Disord.* 1990 Nov;20(3):193-200.

109. Beliles K, Stoudemire A. Psychopharmacologic treatment of depression in the medically ill. *Psychosomatics*. 1998 May-Jun;39(3):S2-19.
110. Benbow SM. Management of depression in the elderly. *Br J Hosp Med*. 1992 Dec 2-1993 Jan 5;48(11):726-31.
111. Bergsholm P, Larsen JL, Rosendahl K, Holsten F. Electroconvulsive therapy and cerebral computed tomography. A prospective study. *Acta Psychiatr Scand*. 1989 Dec;80(6):566-72.
112. Berk M, Copolov DL, Dean O, Lu K, Jeavons S, Schapkaitz I, et al. N-acetyl cysteine for depressive symptoms in bipolar disorder--a double-blind randomized placebo-controlled trial. *Biol Psychiatry*. 2008 Sep 15;64(6):468-75.
113. Berlim MT, Fleck MP, Turecki G. Current trends in the assessment and somatic treatment of resistant/refractory major depression: an overview. *Ann Med*. 2008;40(2):149-59.
114. Berlim MT, Turecki G. What is the meaning of treatment resistant/refractory major depression (TRD)? A systematic review of current randomized trials. *Eur Neuropsychopharmacol*. 2007 Nov;17(11):696-707.
115. Berlim MT, Turecki G. Definition, assessment, and staging of treatment-resistant refractory major depression: a review of current concepts and methods. *Can J Psychiatry*. 2007 Jan;52(1):46-54.
116. Bermack JE, Debonnel G. The role of sigma receptors in depression. *J Pharmacol Sci*. 2005 Mar;97(3):317-36.
117. Berman RM, Narasimhan M, Charney DS. Treatment-refractory depression: definitions and characteristics. *Depress Anxiety*. 1997;5(4):154-64.
118. BERPpohl F, Fregni F, Boggio PS, Thut G, Northoff G, Otachi PT, et al. Effect of low-frequency transcranial magnetic stimulation on an affective go/no-go task in patients with major depression: role of stimulation site and depression severity. *Psychiatry Res*. 2006 Jan 30;141(1):1-13.
119. Berrios GE, Bulbena A, Bakshi N, Dening TR, Jenaway A, Markar H, et al. Feelings of guilt in major depression. Conceptual and psychometric aspects. *Br J Psychiatry*. 1992 Jun;160:781-7.
120. Beutler LE, Engle D, Mohr D, Daldrup RJ, Bergan J, Meredith K, et al. Predictors of differential response to cognitive, experiential, and self-directed psychotherapeutic procedures. *J Consult Clin Psychol*. 1991 Apr;59(2):333-40.
121. Birkenhager TK, Renes JW, Pluijms EM. One-year follow-up after successful ECT: a naturalistic study in depressed inpatients. *J Clin Psychiatry*. 2004 Jan;65(1):87-91.
122. Birkenhager TK, van den Broek WW, Moleman P, Buijij JA. Outcome of a 4-step treatment algorithm for depressed inpatients. *J Clin Psychiatry*. 2006 Aug;67(8):1266-71.
123. Birkenhager TK, van den Broek WW, Mulder PG, Buijij JA, Moleman P. Efficacy and tolerability of tranylcypromine versus phenelzine: a double-blind study in antidepressant-refractory depressed inpatients. *J Clin Psychiatry*. 2004 Nov;65(11):1505-10.
124. Birkenhager TK, Vegt M, Nolen WA. An open study of triiodothyronine augmentation of tricyclic antidepressants in inpatients with refractory depression. *Pharmacopsychiatry*. 1997 Jan;30(1):23-6.
125. Black DW, Goldstein RB, Nasrallah A, Winokur G. The prediction of recovery using a multivariate model in 1471 depressed inpatients. *Eur Arch Psychiatry Clin Neurosci*. 1991;241(1):41-5.
126. Black DW, Winokur G, Nasrallah A. Treatment and outcome in secondary depression: a naturalistic study of 1087 patients. *J Clin Psychiatry*. 1987 Nov;48(11):438-41.
127. Black DW, Winokur G, Nasrallah A. The treatment of depression: electroconvulsive therapy v antidepressants: a naturalistic evaluation of 1,495 patients. *Compr Psychiatry*. 1987 Mar-Apr;28(2):169-82.
128. Blazer D. New concepts in the diagnosis and management of depression. *Compr Ther*. 1988 Apr;14(4):56-60.

129. Blier P, Bergeron R. Effectiveness of pindolol with selected antidepressant drugs in the treatment of major depression. *J Clin Psychopharmacol.* 1995 Jun;15(3):217-22.
130. Blier P, Bergeron R. Early onset of therapeutic action in depression and greater efficacy of antidepressant treatments: are they related? *Int Clin Psychopharmacol.* 1997 Jul;12 Suppl 3:S21-8.
131. Blier P, Bergeron R. The use of pindolol to potentiate antidepressant medication. *J Clin Psychiatry.* 1998;59 Suppl 5:16-23; discussion 4-5.
132. Bobo WV, Shelton RC. Fluoxetine and olanzapine combination therapy in treatment-resistant major depression: review of efficacy and safety data. *Expert Opin Pharmacother.* 2009 Sep;10(13):2145-59.
133. Bobo WV, Shelton RC. Efficacy, safety and tolerability of Symbyax for acute-phase management of treatment-resistant depression. *Expert Rev Neurother.* 2010 May;10(5):651-70.
134. Bocchio-Chiavetto L, Miniussi C, Zanardini R, Gazzoli A, Bignotti S, Specchia C, et al. 5-HTTLPR and BDNF Val66Met polymorphisms and response to rTMS treatment in drug resistant depression. *Neurosci Lett.* 2008 May 30;437(2):130-4.
135. Bocchio-Chiavetto L, Zanardini R, Bortolomasi M, Abate M, Segala M, Giacobuzzi M, et al. Electroconvulsive Therapy (ECT) increases serum Brain Derived Neurotrophic Factor (BDNF) in drug resistant depressed patients. *Eur Neuropsychopharmacol.* 2006 Dec;16(8):620-4.
136. Bodenlos JS, Kose S, Borckardt JJ, Nahas Z, Shaw D, O'Neil PM, et al. Vagus nerve stimulation acutely alters food craving in adults with depression. *Appetite.* 2007 Mar;48(2):145-53.
137. Boggio PS, Fregni F, Berman F, Mansur CG, Rosa M, Rumi DO, et al. Effect of repetitive TMS and fluoxetine on cognitive function in patients with Parkinson's disease and concurrent depression. *Mov Disord.* 2005 Sep;20(9):1178-84.
138. Bohning DE, Lomarev MP, Denslow S, Nahas Z, Shastri A, George MS. Feasibility of vagus nerve stimulation-synchronized blood oxygenation level-dependent functional MRI. *Invest Radiol.* 2001 Aug;36(8):470-9.
139. Bondolfi G, Chautems C, Rochat B, Bertschy G, Baumann P. Non-response to citalopram in depressive patients: pharmacokinetic and clinical consequences of a fluvoxamine augmentation. *Psychopharmacology (Berl).* 1996 Dec;128(4):421-5.
140. Bonne O, Krausz Y, Gorfine M, Karger H, Gelfin Y, Shapira B, et al. Cerebral hypoperfusion in medication resistant, depressed patients assessed by Tc99m HMPAO SPECT. *J Affect Disord.* 1996 Dec 16;41(3):163-71.
141. Bonner D, Howard R. Treatment-resistant depression in the elderly. *Int Psychogeriatr.* 1995;7 Suppl:83-94.
142. Bonnet U. Moclobemide: therapeutic use and clinical studies. *CNS Drug Rev.* 2003 Spring;9(1):97-140.
143. Borckardt JJ, Kozel FA, Anderson B, Walker A, George MS. Vagus nerve stimulation affects pain perception in depressed adults. *Pain Res Manag.* 2005 Spring;10(1):9-14.
144. Bortolomasi M, Minelli A, Fuggetta G, Perini M, Comencini S, Fiaschi A, et al. Long-lasting effects of high frequency repetitive transcranial magnetic stimulation in major depressed patients. *Psychiatry Res.* 2007 Mar 30;150(2):181-6.
145. Bosboom PR, Deijen JB. Age-related cognitive effects of ECT and ECT-induced mood improvement in depressive patients. *Depress Anxiety.* 2006;23(2):93-101.
146. Bosworth HB, Hays JC, George LK, Steffens DC. Psychosocial and clinical predictors of unipolar depression outcome in older adults. *Int J Geriatr Psychiatry.* 2002 Mar;17(3):238-46.
147. Bosworth HB, McQuoid DR, George LK, Steffens DC. Time-to-remission from geriatric depression: psychosocial and clinical factors. *Am J Geriatr Psychiatry.* 2002 Sep-Oct;10(5):551-9.

148. Botteron KN, Geller B. Refractory depression in children and adolescents. *Depress Anxiety*. 1997;5(4):212-23.
149. Bowden CL. Treatment options for bipolar depression. *J Clin Psychiatry*. 2005;66 Suppl 1:3-6.
150. Bradvik L, Berglund M. Long-term treatment and suicidal behavior in severe depression: ECT and antidepressant pharmacotherapy may have different effects on the occurrence and seriousness of suicide attempts. *Depress Anxiety*. 2006;23(1):34-41.
151. Brakemeier EL, Luborzewski A, Danker-Hopfe H, Kathmann N, Bajbouj M. Positive predictors for antidepressant response to prefrontal repetitive transcranial magnetic stimulation (rTMS). *J Psychiatr Res*. 2007 Aug;41(5):395-403.
152. Brakemeier EL, Wilbertz G, Rodax S, Danker-Hopfe H, Zinka B, Zwanzger P, et al. Patterns of response to repetitive transcranial magnetic stimulation (rTMS) in major depression: replication study in drug-free patients. *J Affect Disord*. 2008 May;108(1-2):59-70.
153. Brandon S, Cowley P, McDonald C, Neville P, Palmer R, Wellstood-Eason S. Electroconvulsive therapy: results in depressive illness from the Leicestershire trial. *Br Med J (Clin Res Ed)*. 1984 Jan 7;288(6410):22-5.
154. Bretlau LG, Lunde M, Lindberg L, Unden M, Dissing S, Bech P. Repetitive transcranial magnetic stimulation (rTMS) in combination with escitalopram in patients with treatment-resistant major depression: a double-blind, randomised, sham-controlled trial. *Pharmacopsychiatry* 2008:41-7.
155. Brink CB, Harvey BH, Brand L. Tianeptine: a novel atypical antidepressant that may provide new insights into the biomolecular basis of depression. *Recent Pat CNS Drug Discov*. 2006 Jan;1(1):29-41.
156. Brockington IF, Kendell RE, Wainwright S. Depressed patients with schizophrenic or paranoid symptoms. *Psychol Med*. 1980 Nov;10(4):665-75.
157. Brodaty H, Berle D, Hickie I, Mason C. "Side effects" of ECT are mainly depressive phenomena and are independent of age. *J Affect Disord*. 2001 Oct;66(2-3):237-45.
158. Brodaty H, Hickie I, Mason C, Prenter L. A prospective follow-up study of ECT outcome in older depressed patients. *J Affect Disord*. 2000 Nov;60(2):101-11.
159. Brown AJ. Depression and insulin resistance: applications to polycystic ovary syndrome. *Clin Obstet Gynecol*. 2004 Sep;47(3):592-6.
160. Brusov OS, Fomenko AM, Katasonov AB. Human plasma inhibitors of platelet serotonin uptake and imipramine receptor binding: extraction and heterogeneity. *Biol Psychiatry*. 1985 Mar;20(3):235-44.
161. Bschor T. Therapy-resistant depression. *Expert Rev Neurother*. 2010 Jan;10(1):77-86.
162. Bschor T, Baethge C, Adli M, Eichmann U, Ising M, Uhr M, et al. Association between response to lithium augmentation and the combined DEX/CRH test in major depressive disorder. *J Psychiatr Res*. 2003 Mar-Apr;37(2):135-43.
163. Bschor T, Bauer M. Efficacy and mechanisms of action of lithium augmentation in refractory major depression. *Curr Pharm Des*. 2006;12(23):2985-92.
164. Bschor T, Berghofer A, Strohle A, Kunz D, Adli M, Muller-Oerlinghausen B, et al. How long should the lithium augmentation strategy be maintained? A 1-year follow-up of a placebo-controlled study in unipolar refractory major depression. *J Clin Psychopharmacol*. 2002 Aug;22(4):427-30.
165. Bschor T, Canata B, Muller-Oerlinghausen B, Bauer M. Predictors of response to lithium augmentation in tricyclic antidepressant-resistant depression. *J Affect Disord*. 2001 May;64(2-3):261-5.
166. Bschor T, Lewitzka U, Sasse J, Adli M, Koberle U, Bauer M. Lithium augmentation in treatment-resistant depression: clinical evidence, serotonergic and endocrine mechanisms. *Pharmacopsychiatry*. 2003 Nov;36 Suppl 3:S230-4.

167. Bulbena A, Berrios GE. Cognitive function in the affective disorders: a prospective study. *Psychopathology*. 1993;26(1):6-12.
168. Bundy BD, Hewer W, Andres FJ, Gass P, Sartorius A. Influence of anesthetic drugs and concurrent psychiatric medication on seizure adequacy during electroconvulsive therapy. *J Clin Psychiatry*. 2010 Jun;71(6):775-7.
169. Burke MJ, Husain MM. Concomitant use of vagus nerve stimulation and electroconvulsive therapy for treatment-resistant depression. *J Ect*. 2006 Sep;22(3):218-22.
170. Burton SW. A review of fluvoxamine and its uses in depression. *Int Clin Psychopharmacol*. 1991 Dec;6 Suppl 3:1-17; discussion -21.
171. Bustin J, Rapoport MJ, Krishna M, Matusevich D, Finkelsztein C, Strejilevich S, et al. Are patients' attitudes towards and knowledge of electroconvulsive therapy transcultural? A multi-national pilot study. *Int J Geriatr Psychiatry*. 2008 May;23(5):497-503.
172. Butterfield NN, Graf P, Macleod BA, Ries CR, Zis AP. Propofol reduces cognitive impairment after electroconvulsive therapy. *J Ect*. 2004 Mar;20(1):3-9.
173. Cadieux RJ. Practical management of treatment-resistant depression. *Am Fam Physician*. 1998 Dec;58(9):2059-62.
174. Cain RA. Navigating the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study: practical outcomes and implications for depression treatment in primary care. *Prim Care*. 2007 Sep;34(3):505-19, vi.
175. Calev A, Nigal D, Shapira B, Tubi N, Chazan S, Ben-Yehuda Y, et al. Early and long-term effects of electroconvulsive therapy and depression on memory and other cognitive functions. *J Nerv Ment Dis*. 1991 Sep;179(9):526-33.
176. Caley CF, Weber SS. Paroxetine: a selective serotonin reuptake inhibiting antidepressant. *Ann Pharmacother*. 1993 Oct;27(10):1212-22.
177. Calfa G, Kademian S, Ceschin D, Vega G, Rabinovich GA, Volosin M. Characterization and functional significance of glucocorticoid receptors in patients with major depression: modulation by antidepressant treatment. *Psychoneuroendocrinology*. 2003 Jul;28(5):687-701.
178. Capiello A, McDougale CJ, Delgado PL, Malison RT, Jatlow P, Charney DS, et al. Lithium and desipramine versus desipramine alone in the treatment of severe major depression: a preliminary study. *Int Clin Psychopharmacol*. 1998 Sep;13(5):191-8.
179. Capiello A, McDougale CJ, Malison RT, Heninger GR, Price LH. Yohimbine augmentation of fluvoxamine in refractory depression: a single-blind study. *Biol Psychiatry*. 1995 Dec 1;38(11):765-7.
180. Cardoner N, Pujol J, Vallejo J, Urretavizcaya M, Deus J, Lopez-Sala A, et al. Enlargement of brain cerebrospinal fluid spaces as a predictor of poor clinical outcome in melancholia. *J Clin Psychiatry*. 2003 Jun;64(6):691-7.
181. Carl C, Engelhardt W, Teichmann G, Fuchs G. Open comparative study with treatment-refractory depressed patients: electroconvulsive therapy--anesthetic therapy with isoflurane (preliminary report). *Pharmacopsychiatry*. 1988 Nov;21(6):432-3.
182. Carmody TJ, Rush AJ, Bernstein IH, Brannan S, Husain MM, Trivedi MH. Making clinicians lives easier: guidance on use of the QIDS self-report in place of the MADRS. *J Affect Disord*. 2006 Oct;95(1-3):115-8.
183. Carney RM, Blumenthal JA, Freedland KE, Youngblood M, Veith RC, Burg MM, et al. Depression and late mortality after myocardial infarction in the Enhancing Recovery in Coronary Heart Disease (ENRICHD) study. *Psychosom Med*. 2004 Jul-Aug;66(4):466-74.
184. Carney RM, Freedland KE. Treatment-resistant depression and mortality after acute coronary syndrome. *Am J Psychiatry*. 2009 Apr;166(4):410-7.
185. Carpenter LL. Neurostimulation in resistant depression. *J Psychopharmacol*. 2006 May;20(3 Suppl):35-40.

186. Carpenter LL, Bayat L, Moreno F, Kling MA, Price LH, Tyrka AR, et al. Decreased cerebrospinal fluid concentrations of substance P in treatment-resistant depression and lack of alteration after acute adjunct vagus nerve stimulation therapy. *Psychiatry Res.* 2008 Jan 15;157(1-3):123-9.
187. Carpenter LL, Friehs GM, Price LH. Cervical vagus nerve stimulation for treatment-resistant depression. *Neurosurg Clin N Am.* 2003 Apr;14(2):275-82.
188. Carpenter LL, Jovic Z, Hall JM, Rasmussen SA, Price LH. Mirtazapine augmentation in the treatment of refractory depression. *J Clin Psychiatry.* 1999 Jan;60(1):45-9.
189. Carretero B, Martin MJ, Juan A, Pradana ML, Martin B, Carral M, et al. Low-frequency transcranial magnetic stimulation in patients with fibromyalgia and major depression. *Pain Med.* 2009 May-Jun;10(4):748-53.
190. Carvalho AF, Cavalcante JL, Castelo MS, Lima MC. Augmentation strategies for treatment-resistant depression: a literature review. *J Clin Pharm Ther.* 2007 Oct;32(5):415-28.
191. Carvalho AF, Machado JR, Cavalcante JL. Augmentation strategies for treatment-resistant depression. *Curr Opin Psychiatry.* 2009 Jan;22(1):7-12.
192. Carvalho LA, Juruena MF, Papadopoulos AS, Poon L, Kerwin R, Cleare AJ, et al. Clomipramine in vitro reduces glucocorticoid receptor function in healthy subjects but not in patients with major depression. *Neuropsychopharmacology.* 2008 Dec;33(13):3182-9.
193. Casey DA. Depression in the elderly. *South Med J.* 1994 May;87(5):559-63.
194. Casey P, Meagher D, Butler E. Personality, functioning, and recovery from major depression. *J Nerv Ment Dis.* 1996 Apr;184(4):240-5.
195. Cassidy F. Antidepressant treatment practice in the face of STAR*D and STEP-BD. *Bipolar Disord.* 2008 Dec;10(8):973-4.
196. Cassidy F, Murry E, Weiner RD, Carroll BJ. Lack of relapse with tryptophan depletion following successful treatment with ECT. *Am J Psychiatry.* 1997 Aug;154(8):1151-2.
197. Cassidy F, Weiner RD, Cooper TB, Carroll BJ. Antidepressant response to electroconvulsive therapy is sustained after catecholamine depletion. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009 Aug 1;33(5):872-4.
198. Chaimowitz GA, Links PS, Padgett RW, Carr AC. Treatment-resistant depression: a survey of practice habits of Canadian psychiatrists. *Can J Psychiatry.* 1991 Jun;36(5):353-6.
199. Chambers AS, Allen JJ. Vagal tone as an indicator of treatment response in major depression. *Psychophysiology.* 2002 Nov;39(6):861-4.
200. Charney DS, Price LH, Heninger GR. Desipramine-yohimbine combination treatment of refractory depression. Implications for the beta-adrenergic receptor hypothesis of antidepressant action. *Arch Gen Psychiatry.* 1986 Dec;43(12):1155-61.
201. Chavel SM, Westerveld M, Spencer S. Long-term outcome of vagus nerve stimulation for refractory partial epilepsy. *Epilepsy Behav.* 2003 Jun;4(3):302-9.
202. Chehil S, Devarajan S, Dursun SM. Pharmacologic management of refractory depression. *Can Fam Physician.* 2001 Jan;47:50-2.
203. Chen YC, Lin WW, Chen YJ, Mao WC, Hung YJ. Antidepressant effects on insulin sensitivity and proinflammatory cytokines in the depressed males. *Mediators Inflamm.* 2010;2010:573594.
204. Chen YC, Shen YC, Hung YJ, Chou CH, Yeh CB, Perng CH. Comparisons of glucose-insulin homeostasis following maprotiline and fluoxetine treatment in depressed males. *J Affect Disord.* 2007 Nov;103(1-3):257-61.
205. Chistyakov AV, Kaplan B, Rubichek O, Kreinin I, Koren D, Feinsod M, et al. Antidepressant effects of different schedules of repetitive transcranial magnetic stimulation vs. clomipramine in patients with major depression: relationship to changes in cortical excitability. *Int J Neuropsychopharmacol.* 2005 Jun;8(2):223-33.

206. Chistyakov AV, Kaplan B, Rubicsek O, Kreinin I, Koren D, Hafner H, et al. Effect of electroconvulsive therapy on cortical excitability in patients with major depression: a transcranial magnetic stimulation study. *Clin Neurophysiol*. 2005 Feb;116(2):386-92.
207. Chistyakov AV, Rubicsek O, Kaplan B, Zaaroor M, Klein E. Safety, tolerability and preliminary evidence for antidepressant efficacy of theta-burst transcranial magnetic stimulation in patients with major depression. *Int J Neuropsychopharmacol*. 2010 Apr;13(3):387-93.
208. Choi MJ, Kang RH, Lim SW, Oh KS, Lee MS. Brain-derived neurotrophic factor gene polymorphism (Val66Met) and citalopram response in major depressive disorder. *Brain Res*. 2006 Nov 6;1118(1):176-82.
209. Chow TW, Mendez MF. Goals in symptomatic pharmacologic management of frontotemporal lobar degeneration. *Am J Alzheimers Dis Other Dement*. 2002 Sep-Oct;17(5):267-72.
210. Cinar S, Oude Voshaar RC, Janzing JG, Birkenhager TK, Buitelaar JK, van den Broek WW. The course of depressive symptoms in unipolar depressive disorder during electroconvulsive therapy: a latent class analysis. *J Affect Disord*. 2010 Jul;124(1-2):141-7.
211. Cipriani A, Smith K, Burgess S, Carney S, Goodwin G, Geddes J. Lithium versus antidepressants in the long-term treatment of unipolar affective disorder. *Cochrane Database Syst Rev*. 2006(4):CD003492.
212. Clark CP, Alexopoulos GS, Kaplan J. Prolactin release and clinical response to electroconvulsive therapy in depressed geriatric inpatients: a preliminary report. *Convuls Ther*. 1995 Mar;11(1):24-31.
213. Coffey CE, Figiel GS, Djang WT, Sullivan DC, Herfkens RJ, Weiner RD. Effects of ECT on brain structure: a pilot prospective magnetic resonance imaging study. *Am J Psychiatry*. 1988 Jun;145(6):701-6.
214. Coffey CE, Figiel GS, Weiner RD, Saunders WB. Caffeine augmentation of ECT. *Am J Psychiatry*. 1990 May;147(5):579-85.
215. Coffey CE, Weiner RD, Djang WT, Figiel GS, Soady SA, Patterson LJ, et al. Brain anatomic effects of electroconvulsive therapy. A prospective magnetic resonance imaging study. *Arch Gen Psychiatry*. 1991 Nov;48(11):1013-21.
216. Cohen LJ. A managed care perspective of individualized care. *J Manag Care Pharm*. 2004 Mar;10(2 Suppl):S16-21.
217. Cohen MR, Swartz CM. Absence of nimodipine premedication effect on memory after electroconvulsive therapy. *Neuropsychobiology*. 1990;24(4):165-8.
218. Cohen RB, Brunoni AR, Boggio PS, Fregni F. Clinical predictors associated with duration of repetitive transcranial magnetic stimulation treatment for remission in bipolar depression: a naturalistic study. *J Nerv Ment Dis*. 2010 Sep;198(9):679-81.
219. Cohen Y, Feldinger E, Ogorek D, Weinbroum AA. Increased propofol requirement during succeeding administrations for electroconvulsive therapy. *J Clin Anesth*. 2004 Jun;16(4):282-5.
220. Cohn JB. Triazolam treatment of insomnia in depressed patients taking tricyclics. *J Clin Psychiatry*. 1983 Nov;44(11):401-6.
221. Cohrs S, Tergau F, Korn J, Becker W, Hajak G. Suprathreshold repetitive transcranial magnetic stimulation elevates thyroid-stimulating hormone in healthy male subjects. *J Nerv Ment Dis*. 2001 Jun;189(6):393-7.
222. Cohrs S, Tergau F, Riech S, Kastner S, Paulus W, Ziemann U, et al. High-frequency repetitive transcranial magnetic stimulation delays rapid eye movement sleep. *Neuroreport*. 1998 Oct 26;9(15):3439-43.
223. Coleman EA, Sackeim HA, Prudic J, Devanand DP, McElhiney MC, Moody BJ. Subjective memory complaints prior to and following electroconvulsive therapy. *Biol Psychiatry*. 1996 Mar 1;39(5):346-56.
224. Conca A, Koppi S, König P, Swoboda E, Krecke N. Transcranial magnetic stimulation: a novel antidepressive strategy? *Neuropsychobiology*. 1996;34(4):204-7.

225. Conway CR, Sheline YI, Chibnall JT, George MS, Fletcher JW, Mintun MA. Cerebral blood flow changes during vagus nerve stimulation for depression. *Psychiatry Res.* 2006 Mar 31;146(2):179-84.
226. Cook IA, Leuchter AF, Witte E, Abrams M, Uijtdehaage SH, Stubbeman W, et al. Neurophysiologic predictors of treatment response to fluoxetine in major depression. *Psychiatry Res.* 1999 Mar 22;85(3):263-73.
227. Cooper AJ, Finlayson R, Velamoor VR, Magnus RV, Cernovsky Z. Effects of ECT on prolactin, LH, FSH and testosterone in males with major depressive illness. *Can J Psychiatry.* 1989 Nov;34(8):814-7.
228. Copeland JR. Depressive illness and morbid distress. Onset and development data examined against five-year outcome. *Br J Psychiatry.* 1985 Mar;146:297-307.
229. Coplan JD, Tiffon L, Gorman JM. Therapeutic strategies for the patient with treatment-resistant anxiety. *J Clin Psychiatry.* 1993 May;54 Suppl:69-74.
230. Coppen A. Depression as a lethal disease: prevention strategies. *J Clin Psychiatry.* 1994 Apr;55 Suppl:37-45.
231. Coppen A. Lithium in unipolar depression and the prevention of suicide. *J Clin Psychiatry.* 2000;61 Suppl 9:52-6.
232. Coppen A, Abou-Saleh MT, Milln P, Bailey J, Metcalfe M, Burns BH, et al. Lithium continuation therapy following electroconvulsive therapy. *Br J Psychiatry.* 1981 Oct;139:284-7.
233. Corcoran C, Connor TJ, O'Keane V, Garland MR. The effects of vagus nerve stimulation on pro- and anti-inflammatory cytokines in humans: a preliminary report. *Neuroimmunomodulation.* 2005;12(5):307-9.
234. Corcoran CD, Thomas P, Phillips J, O'Keane V. Vagus nerve stimulation in chronic treatment-resistant depression: preliminary findings of an open-label study. *Br J Psychiatry.* 2006 Sep;189:282-3.
235. Corey-Lisle PK, Birnbaum HG, Greenberg PE, Marynchenko MB, Claxton AJ. Identification of a claims data "signature" and economic consequences for treatment-resistant depression. *J Clin Psychiatry.* 2002 Aug;63(8):717-26.
236. Corya SA, Andersen SW, Detke HC, Kelly LS, Van Campen LE, Sanger TM, et al. Long-term antidepressant efficacy and safety of olanzapine/fluoxetine combination: a 76-week open-label study. *J Clin Psychiatry.* 2003 Nov;64(11):1349-56.
237. Corya SA, Williamson D, Sanger TM, Briggs SD, Case M, Tollefson G. A randomized, double-blind comparison of olanzapine/fluoxetine combination, olanzapine, fluoxetine, and venlafaxine in treatment-resistant depression. *Depress Anxiety* 2006:364-72.
238. Coryell W, Endicott J, Keller M. Outcome of patients with chronic affective disorder: a five-year follow-up. *Am J Psychiatry.* 1990 Dec;147(12):1627-33.
239. Coryell W, Noyes R, Clancy J. Panic disorder and primary unipolar depression. A comparison of background and outcome. *J Affect Disord.* 1983 Nov;5(4):311-7.
240. Coryell W, Tsuang MT. Primary unipolar depression and the prognostic importance of delusions. *Arch Gen Psychiatry.* 1982 Oct;39(10):1181-4.
241. Coryell W, Zimmerman M. Outcome following ECT for primary unipolar depression: a test of newly proposed response predictors. *Am J Psychiatry.* 1984 Jul;141(7):862-7.
242. Cowen PJ. Depression resistant to tricyclic antidepressants. *Bmj.* 1988 Aug 13;297(6646):435-6.
243. Cowen PJ. Commentary on STAR*D: a summary and UK perspective. *J Psychopharmacol.* 2009 Aug;23(6):618-9; discussion 22-4.
244. Cowen PJ, McCance SL, Cohen PR, Julier DL. Lithium increases 5-HT-mediated neuroendocrine responses in tricyclic resistant depression. *Psychopharmacology (Berl).* 1989;99(2):230-2.
245. Cowen PJ, McCance SL, Ware CJ, Cohen PR, Chalmers JS, Julier DL. Lithium in tricyclic-resistant depression. Correlation of increased brain 5-HT function with clinical outcome. *Br J Psychiatry.* 1991 Sep;159:341-6.

246. Craig TJ, Grossman S, Bromet EJ, Fochtmann LJ, Carlson GA. Medication use patterns and two-year outcome in first-admission patients with major depressive disorder with psychotic features. *Compr Psychiatry*. 2007 Nov-Dec;48(6):497-503.
247. Crebbin K, Mitford E, Paxton R, Turkington D. First-episode psychosis: an epidemiological survey comparing psychotic depression with schizophrenia. *J Affect Disord*. 2008 Jan;105(1-3):117-24.
248. Crevits L, Van den Abbeele D, Audenaert K, Goethals M, Dierick M. Effect of repetitive transcranial magnetic stimulation on saccades in depression: a pilot study. *Psychiatry Res*. 2005 Jun 15;135(2):113-9.
249. Criado JM, Fernandez A, Ortiz T. Long-term effects of electroconvulsive therapy on episodic memory. *Actas Esp Psiquiatr*. 2007 Jan-Feb;35(1):40-6.
250. Cronholm B, Ottosson JO. Experimental studies of the therapeutic action of electroconvulsive therapy in endogenous depression. The role of the electrical stimulation and of the seizure studied by variation of stimulus intensity and modification by lidocaine of seizure discharge. *Convuls Ther*. 1996 Sep;12(3):172-94.
251. Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. *J Clin Psychiatry*. 2007 Jun;68(6):935-40.
252. Croughan JL, Secunda SK, Katz MM, Robins E, Mendels J, Swann A, et al. Sociodemographic and prior clinical course characteristics associated with treatment response in depressed patients. *J Psychiatr Res*. 1988;22(3):227-37.
253. Crow TJ, Johnstone EC. Controlled trials of electroconvulsive therapy. *Ann N Y Acad Sci*. 1986;462:12-29.
254. Croxtall JD, Scott LJ. Olanzapine/fluoxetine: a review of its use in patients with treatment-resistant major depressive disorder. *CNS Drugs*. 2010 Mar 1;24(3):245-62.
255. Cullen M, Mitchell P, Brodaty H, Boyce P, Parker G, Hickie I, et al. Carbamazepine for treatment-resistant melancholia. *J Clin Psychiatry*. 1991 Nov;52(11):472-6.
256. Culpepper L. Why do you need to move beyond first-line therapy for major depression? *J Clin Psychiatry*. 2010;71 Suppl 1:4-9.
257. Curran S. Effect of paroxetine on seizure length during electroconvulsive therapy. *Acta Psychiatr Scand*. 1995 Sep;92(3):239-40.
258. Currier MB, Murray GB, Welch CC. Electroconvulsive therapy for post-stroke depressed geriatric patients. *J Neuropsychiatry Clin Neurosci*. 1992 Spring;4(2):140-4.
259. Dailly E, Chenu F, Renard CE, Bourin M. Dopamine, depression and antidepressants. *Fundam Clin Pharmacol*. 2004 Dec;18(6):601-7.
260. Dallah A, Fontaine R, Ontiveros A, Elie R. Lithium carbonate augmentation of desipramine in refractory depression. *Can J Psychiatry*. 1990 Oct;35(7):608-11.
261. Dalton EJ, Rotondi D, Levitan RD, Kennedy SH, Brown GM. Use of slow-release melatonin in treatment-resistant depression. *J Psychiatry Neurosci*. 2000 Jan;25(1):48-52.
262. Daly RJ, Duggan PF, Bracken PJ, Doonan HJ, Kelleher NJ. Plasma levels of beta-endorphin in depressed patients with and without pain. *Br J Psychiatry*. 1987 Feb;150:224-7.
263. Dang T, Avery DH, Russo J. Within-session mood changes from TMS in depressed patients. *J Neuropsychiatry Clin Neurosci*. 2007 Fall;19(4):458-63.
264. Daniel WF, Crovitz HF, Weiner RD. Perceptual learning with right unilateral versus bilateral electroconvulsive therapy. *Br J Psychiatry*. 1984 Oct;145:394-400.
265. Dannon PN, Dolberg OT, Schreiber S, Grunhaus L. Three and six-month outcome following courses of either ECT or rTMS in a population of severely depressed individuals--preliminary report. *Biol Psychiatry*. 2002 Apr 15;51(8):687-90.

266. DasGupta K. Treatment of depression in elderly patients: recent advances. *Arch Fam Med*. 1998 May-Jun;7(3):274-80.
267. Davidson JR. First-line pharmacotherapy approaches for generalized anxiety disorder. *J Clin Psychiatry*. 2009;70 Suppl 2:25-31.
268. Dawson R, Lavori PW, Coryell WH, Endicott J, Keller MB. Course of treatment received by depressed patients. *J Psychiatr Res*. 1999 May-Jun;33(3):233-42.
269. De Fruyt F, Van Leeuwen K, Bagby RM, Rolland JP, Rouillon F. Assessing and interpreting personality change and continuity in patients treated for major depression. *Psychol Assess*. 2006 Mar;18(1):71-80.
270. de Groot MH, Nolen WA, Huijsman AM, Bouvy PF. Lateralized neuropsychological functioning in depressive patients before and after drug therapy. *Biol Psychiatry*. 1996 Dec 15;40(12):1282-7.
271. De Montigny C. Enhancement of the 5-HT neurotransmission by antidepressant treatments. *J Physiol (Paris)*. 1981;77(2-3):455-61.
272. de Montigny C. Lithium addition in treatment-resistant depression. *Int Clin Psychopharmacol*. 1994 Jun;9 Suppl 2:31-5.
273. de Montigny C, Cournoyer G, Morissette R, Langlois R, Caille G. Lithium carbonate addition in tricyclic antidepressant-resistant unipolar depression. Correlations with the neurobiologic actions of tricyclic antidepressant drugs and lithium ion on the serotonin system. *Arch Gen Psychiatry*. 1983 Dec;40(12):1327-34.
274. De Montigny C, Grunberg F, Mayer A, Deschenes JP. Lithium induces rapid relief of depression in tricyclic antidepressant drug non-responders. *Br J Psychiatry*. 1981 Mar;138:252-6.
275. de Vreede IM, Burger H, van Vliet IM. Prediction of response to ECT with routinely collected data in major depression. *J Affect Disord*. 2005 Jun;86(2-3):323-7.
276. DeBattista C. Augmentation and combination strategies for depression. *J Psychopharmacol*. 2006 May;20(3 Suppl):11-8.
277. DeBattista C, DeBattista K. Safety considerations of the use of second generation antipsychotics in the treatment of major depression: extrapyramidal and metabolic side effects. *Curr Drug Saf*. 2010 Jul 2;5(3):263-6.
278. DeBattista C, Hawkins J. Utility of atypical antipsychotics in the treatment of resistant unipolar depression. *CNS Drugs*. 2009;23(5):369-77.
279. DeBattista C, Lembke A. Update on augmentation of antidepressant response in resistant depression. *Curr Psychiatry Rep*. 2005 Dec;7(6):435-40.
280. DeBattista C, Solvason HB, Poirier J, Kendrick E, Schatzberg AF. A prospective trial of bupropion SR augmentation of partial and non-responders to serotonergic antidepressants. *J Clin Psychopharmacol*. 2003 Feb;23(1):27-30.
281. Dechant KL, Clissold SP. Paroxetine. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in depressive illness. *Drugs*. 1991 Feb;41(2):225-53.
282. Defrin R, Grunhaus L, Zamir D, Zeilig G. The effect of a series of repetitive transcranial magnetic stimulations of the motor cortex on central pain after spinal cord injury. *Arch Phys Med Rehabil*. 2007 Dec;88(12):1574-80.
283. Delgado PL, Price LH, Charney DS, Heninger GR. Efficacy of fluvoxamine in treatment-refractory depression. *J Affect Disord*. 1988 Jul-Aug;15(1):55-60.
284. Delgado PL, Price LH, Miller HL, Salomon RM, Aghajanian GK, Heninger GR, et al. Serotonin and the neurobiology of depression. Effects of tryptophan depletion in drug-free depressed patients. *Arch Gen Psychiatry*. 1994 Nov;51(11):865-74.
285. d'Elia G, Frederiksen SO. ACTH4-10 and memory in ECT-treated patients and untreated controls. II. Effect on retrieval. *Acta Psychiatr Scand*. 1980 Nov;62(5):429-35.
286. d'Elia G, Frederiksen SO. ACTH4-10 and memory in ECT-treated and untreated patients. I. Effect on consolidation. *Acta Psychiatr Scand*. 1980 Nov;62(5):418-28.

287. Delva NJ, Brunet DG, Hawken ER, Kesteven RM, Lawson JS, Lywood DW, et al. Characteristics of responders and nonresponders to brief-pulse right unilateral ECT in a controlled clinical trial. *J Ect*. 2001 Jun;17(2):118-23.
288. DeMet EM, Bell KM, Reist C, Gerner RH, Chicz-DeMet A. Seasonal changes in cyanoimipramine specific platelet 3H-imipramine binding in depression. *Psychiatry Res*. 1990 Dec;34(3):315-29.
289. DeMet EM, Chicz-DeMet A. Subclasses of platelet 3H-imipramine binding sites. *Psychiatry Res*. 1990 Dec;34(3):293-302.
290. Demirtas-Tatlidede A, Mechanic-Hamilton D, Press DZ, Pearlman C, Stern WM, Thall M, et al. An open-label, prospective study of repetitive transcranial magnetic stimulation (rTMS) in the long-term treatment of refractory depression: reproducibility and duration of the antidepressant effect in medication-free patients. *J Clin Psychiatry*. 2008 Jun;69(6):930-4.
291. Dessauer M, Goetze U, Tolle R. Periodic sleep deprivation in drug-refractory depression. *Neuropsychobiology*. 1985;13(3):111-6.
292. Devanand DP, Dwork AJ, Hutchinson ER, Bolwig TG, Sackeim HA. Does ECT alter brain structure? *Am J Psychiatry*. 1994 Jul;151(7):957-70.
293. Devanand DP, Fitzsimons L, Prudic J, Sackeim HA. Subjective side effects during electroconvulsive therapy. *Convuls Ther*. 1995 Dec;11(4):232-40.
294. Devanand DP, Lisanby S, Lo ES, Fitzsimons L, Cooper TB, Halbreich U, et al. Effects of electroconvulsive therapy on plasma vasopressin and oxytocin. *Biol Psychiatry*. 1998 Oct 1;44(7):610-6.
295. Devanand DP, Sackeim HA, Prudic J. Electroconvulsive therapy in the treatment-resistant patient. *Psychiatr Clin North Am*. 1991 Dec;14(4):905-23.
296. Devanand DP, Verma AK, Tirumalasetti F, Sackeim HA. Absence of cognitive impairment after more than 100 lifetime ECT treatments. *Am J Psychiatry*. 1991 Jul;148(7):929-32.
297. Dew R, McCall WV. Efficiency of outpatient ECT. *J Ect*. 2004 Mar;20(1):24-5.
298. Dick PH, Sweeney ML, Crombie IK. Controlled comparison of day-patient and out-patient treatment for persistent anxiety and depression. *Br J Psychiatry*. 1991 Jan;158:24-7.
299. Dietrich DE, Emrich HM. The use of anticonvulsants to augment antidepressant medication. *J Clin Psychiatry*. 1998;59 Suppl 5:51-8; discussion 9.
300. Dinan TG. Lithium augmentation in sertraline-resistant depression: a preliminary dose-response study. *Acta Psychiatr Scand*. 1993 Oct;88(4):300-1.
301. Dinan TG, Barry S. A comparison of electroconvulsive therapy with a combined lithium and tricyclic combination among depressed tricyclic nonresponders. *Acta Psychiatr Scand*. 1989 Jul;80(1):97-100.
302. Dinan TG, Lavelle E, Cooney J, Burnett F, Scott L, Dash A, et al. Dexamethasone augmentation in treatment-resistant depression. *Acta Psychiatr Scand*. 1997 Jan;95(1):58-61.
303. Dinan TG, Mobayed M. Treatment resistance of depression after head injury: a preliminary study of amitriptyline response. *Acta Psychiatr Scand*. 1992 Apr;85(4):292-4.
304. Dodd S, Berk M. Olanzapine/fluoxetine combination for treatment-resistant depression: efficacy and clinical utility. *Expert Rev Neurother*. 2008 Sep;8(9):1299-306.
305. Dodd S, Horgan D, Malhi GS, Berk M. To combine or not to combine? A literature review of antidepressant combination therapy. *J Affect Disord*. 2005 Dec;89(1-3):1-11.
306. Dombrowski AY, Mulsant BH, Haskett RF, Prudic J, Begley AE, Sackeim HA. Predictors of remission after electroconvulsive therapy in unipolar major depression. *J Clin Psychiatry*. 2005 Aug;66(8):1043-9.
307. Dording CM. Antidepressant augmentation and combinations. *Psychiatr Clin North Am*. 2000 Dec;23(4):743-55.

308. Doree JP, Des Rosiers J, Lew V, Gendron A, Elie R, Stip E, et al. Quetiapine augmentation of treatment-resistant depression: a comparison with lithium. *Curr Med Res Opin.* 2007 Feb;23(2):333-41.
309. Dowson JH. MAO inhibitors in mental disease: their current status. *J Neural Transm Suppl.* 1987;23:121-38.
310. Dragasevic N, Potrebic A, Damjanovic A, Stefanova E, Kostic VS. Therapeutic efficacy of bilateral prefrontal slow repetitive transcranial magnetic stimulation in depressed patients with Parkinson's disease: an open study. *Mov Disord.* 2002 May;17(3):528-32.
311. Dratcu L, Calil HM. The dexamethasone suppression test: its relationship to diagnoses, severity of depression and response to treatment. *Prog Neuropsychopharmacol Biol Psychiatry.* 1989;13(1-2):99-117.
312. Dubovsky SL, Buzan R, Thomas M, Kassner C, Cullum CM. Nicardipine improves the antidepressant action of ECT but does not improve cognition. *J Ect.* 2001 Mar;17(1):3-10.
313. Dubovsky SL, Christiano J, Daniell LC, Franks RD, Murphy J, Adler L, et al. Increased platelet intracellular calcium concentration in patients with bipolar affective disorders. *Arch Gen Psychiatry.* 1989 Jul;46(7):632-8.
314. Dubovsky SL, Thomas M. Psychotic depression: advances in conceptualization and treatment. *Hosp Community Psychiatry.* 1992 Dec;43(12):1189-98.
315. Dudley DL, Volberding N, Loebel P. Intravenous chlorimipramine and refractory depression. *Gen Hosp Psychiatry.* 1980 Mar;2(1):61-4.
316. Dunner DL. Therapeutic considerations in treating depression in the elderly. *J Clin Psychiatry.* 1994 Dec;55 Suppl:48-58; discussion 9-60.
317. Dunner DL, Amsterdam JD, Shelton RC, Loebel A, Romano SJ. Efficacy and tolerability of adjunctive ziprasidone in treatment-resistant depression: a randomized, open-label, pilot study. *J Clin Psychiatry.* 2007 Jul;68(7):1071-7.
318. Dursun SM, Devarajan S, Kutcher S. The 'dalhousie serotonin cocktail' for treatment-resistant major depressive disorder. *J Psychopharmacol.* 2001 Jun;15(2):136-8.
319. Dursun SM, Patel JK, Drybala T, Shinkwin R, Drybala G, Reveley MA. Effects of antidepressant treatments on first-ECT seizure duration in depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2001 Feb;25(2):437-43.
320. Dziedzicka-Wasylewska M, Rogoz Z, Solich J, Dudek D, Wrobel A, Zieba A. Effect of joint administration of imipramine and amantadine on binding of [3H]7-OH-DPAT to dopamine D3 receptors in peripheral blood lymphocytes of the patients with drug-resistant unipolar depression. *Pol J Pharmacol.* 2002 Nov-Dec;54(6):703-6.
321. Ebert D, Albert R, May A, Stosiek I, Kaschka W. Combined SSRI-RIMA treatment in refractory depression. Safety data and efficacy. *Psychopharmacology (Berl).* 1995 Jun;119(3):342-4.
322. Eby GA, 3rd, Eby KL. Magnesium for treatment-resistant depression: a review and hypothesis. *Med Hypotheses.* 2010 Apr;74(4):649-60.
323. Egberts AC, Lenderink AW, de Koning FH, Leufkens HG. Channeling of three newly introduced antidepressants to patients not responding satisfactorily to previous treatment. *J Clin Psychopharmacol.* 1997 Jun;17(3):149-55.
324. Eggar R, Spencer A, Anderson D, Hiller L. Views of elderly patients on cardiopulmonary resuscitation before and after treatment for depression. *Int J Geriatr Psychiatry.* 2002 Feb;17(2):170-4.
325. Ehnvall A, Sjogren M, Zachrisson OC, Agren H. Lifetime burden of mood swings and activation of brain norepinephrine turnover in patients with treatment-refractory depressive illness. *J Affect Disord.* 2003 Apr;74(2):185-9.
326. Eichhammer P, Kharraz A, Wiegand R, Langguth B, Frick U, Aigner JM, et al. Sleep deprivation in depression stabilizing antidepressant effects by repetitive transcranial magnetic stimulation. *Life Sci.* 2002 Mar 1;70(15):1741-9.

327. El Khoury A, Johnson L, Aberg-Wistedt A, Stain-Malmgren R. Effects of long-term lithium treatment on monoaminergic functions in major depression. *Psychiatry Res.* 2001 Dec 15;105(1-2):33-44.
328. El Mansari M, Guiard BP, Chernoloz O, Ghanbari R, Katz N, Blier P. Relevance of norepinephrine-dopamine interactions in the treatment of major depressive disorder. *CNS Neurosci Ther.* 2010 Jun;16(3):e1-17.
329. Elger G, Hoppe C, Falkai P, Rush AJ, Elger CE. Vagus nerve stimulation is associated with mood improvements in epilepsy patients. *Epilepsy Res.* 2000 Dec;42(2-3):203-10.
330. Elliott RL. Depression in primary care. *Ethn Dis.* 2007 Spring;17(2 Suppl 2):S2-28-33.
331. Engelhardt W, Carl G, Hartung E. Intra-individual open comparison of burst-suppression-isoflurane-anaesthesia versus electroconvulsive therapy in the treatment of severe depression. *Eur J Anaesthesiol.* 1993 Mar;10(2):113-8.
332. Eranti SV, Mogg AJ, Pluck GC, Landau S, McLoughlin DM. Methohexitone, propofol and etomidate in electroconvulsive therapy for depression: a naturalistic comparison study. *J Affect Disord.* 2009 Feb;113(1-2):165-71.
333. Erinosh O, Ayonrinde A. A cross-national comparison of patterns of utilization and psychiatric care. *Int J Soc Psychiatry.* 1981 Winter;27(4):289-96.
334. Eschweiler GW, Vonthein R, Bode R, Huell M, Conca A, Peters O, et al. Clinical efficacy and cognitive side effects of bifrontal versus right unilateral electroconvulsive therapy (ECT): a short-term randomised controlled trial in pharmaco-resistant major depression. *J Affect Disord.* 2007 Aug;101(1-3):149-57.
335. Ezzat DH, Ibraheem MM, Makhawy B. The effect of Piracetam on ECT--induced memory disturbances. *Br J Psychiatry.* 1985 Dec;147:720-1.
336. Fava GA. Can long-term treatment with antidepressant drugs worsen the course of depression? *J Clin Psychiatry.* 2003 Feb;64(2):123-33.
337. Fava GA, Park SK, Sonino N. Treatment of recurrent depression. *Expert Rev Neurother.* 2006 Nov;6(11):1735-40.
338. Fava GA, Savron G, Grandi S, Rafanelli C. Cognitive-behavioral management of drug-resistant major depressive disorder. *J Clin Psychiatry.* 1997 Jun;58(6):278-82; quiz 83-4.
339. Fava M. New approaches to the treatment of refractory depression. *J Clin Psychiatry.* 2000;61 Suppl 1:26-32.
340. Fava M. Augmentation and combination strategies in treatment-resistant depression. *J Clin Psychiatry.* 2001;62 Suppl 18:4-11.
341. Fava M. Diagnosis and definition of treatment-resistant depression. *Biol Psychiatry.* 2003 Apr 15;53(8):649-59.
342. Fava M. Augmentation and combination strategies for complicated depression. *J Clin Psychiatry.* 2009 Nov;70(11):e40.
343. Fava M. Partial responders to antidepressant treatment: switching strategies. *J Clin Psychiatry.* 2009 Jul;70(7):e24.
344. Fava M. Switching treatments for complicated depression. *J Clin Psychiatry.* 2010 Feb;71(2):e04.
345. Fava M, Davidson KG. Definition and epidemiology of treatment-resistant depression. *Psychiatr Clin North Am.* 1996 Jun;19(2):179-200.
346. Fava M, Papakostas GI, Petersen T, Mahal Y, Quitkin F, Stewart J, et al. Switching to bupropion in fluoxetine-resistant major depressive disorder. *Ann Clin Psychiatry.* 2003 Mar;15(1):17-22.
347. Fava M, Rosenbaum JF, McGrath PJ, Stewart JW, Amsterdam JD, Quitkin FM. Lithium and tricyclic augmentation of fluoxetine treatment for resistant major depression: a double-blind, controlled study. *Am J Psychiatry.* 1994 Sep;151(9):1372-4.
348. Fava M, Rush AJ, Wisniewski SR, Nierenberg AA, Alpert JE, McGrath PJ, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry.* 2006;163:72-77.

349. Fawcett J. Compliance: definitions and key issues. *J Clin Psychiatry*. 1995;56 Suppl 1:4-8; discussion 9-10.
350. Fawcett JA. Lithium combinations in acute and maintenance treatment of unipolar and bipolar depression. *J Clin Psychiatry*. 2003;64 Suppl 5:32-7.
351. Feighner JP. The role of venlafaxine in rational antidepressant therapy. *J Clin Psychiatry*. 1994 Sep;55 Suppl A:62-8; discussion 9-70, 98-100.
352. Feighner JP, Boyer WF, Tyler DL, Neborsky RJ. Adverse consequences of fluoxetine-MAOI combination therapy. *J Clin Psychiatry*. 1990 Jun;51(6):222-5.
353. Feighner JP, Sverdlow L, Hlavka J, Nicolau G, Cartwright K, Freed JS. Clinical effect of nemifitide, a novel pentapeptide antidepressant, in the treatment of severely depressed refractory patients. *Int Clin Psychopharmacol*. 2008 Jan;23(1):29-35.
354. Fekadu A, Wooderson S, Donaldson C, Markopoulou K, Masterson B, Poon L, et al. A multidimensional tool to quantify treatment resistance in depression: the Maudsley staging method. *J Clin Psychiatry*. 2009 Feb;70(2):177-84.
355. Fekadu A, Wooderson SC, Markopoulou K, Donaldson C, Papadopoulos A, Cleare AJ. What happens to patients with treatment-resistant depression? A systematic review of medium to long term outcome studies. *J Affect Disord*. 2009 Jul;116(1-2):4-11.
356. Fekadu A, Wooderson SC, Markopoulou K, Cleare AJ. The Maudsley Staging Method for treatment-resistant depression: prediction of longer-term outcome and persistence of symptoms. *J Clin Psychiatry*. 2009 Jul;70(7):952-7.
357. Feske U, Mulsant BH, Pilkonis PA, Soloff P, Dolata D, Sackeim HA, et al. Clinical outcome of ECT in patients with major depression and comorbid borderline personality disorder. *Am J Psychiatry*. 2004 Nov;161(11):2073-80.
358. Figiel GS, Coffey CE, Djang WT, Hoffman G, Jr., Doraiswamy PM. Brain magnetic resonance imaging findings in ECT-induced delirium. *J Neuropsychiatry Clin Neurosci*. 1990 Winter;2(1):53-8.
359. Figiel GS, DeLeo B, Zorumski CF, Baker K, Goewert A, Jarvis M, et al. Combined use of labetalol and nifedipine in controlling the cardiovascular response from ECT. *J Geriatr Psychiatry Neurol*. 1993 Jan-Mar;6(1):20-4.
360. Fink M, Rush AJ, Knapp R, Rasmussen K, Mueller M, Rummans TA, et al. DSM melancholic features are unreliable predictors of ECT response: a CORE publication. *J Ect*. 2007 Sep;23(3):139-46.
361. Fitzgerald P. Is it time to introduce repetitive transcranial magnetic stimulation into standard clinical practice for the treatment of depressive disorders? *Aust N Z J Psychiatry*. 2003 Feb;37(1):5-11; discussion 2-4.
362. Fitzgerald P, O'Brien SM, Scully P, Rijkers K, Scott LV, Dinan TG. Cutaneous glucocorticoid receptor sensitivity and pro-inflammatory cytokine levels in antidepressant-resistant depression. *Psychol Med*. 2006 Jan;36(1):37-43.
363. Fitzgerald PB, Benitez J, de Castella A, Daskalakis ZJ, Brown TL, Kulkarni J. A randomized, controlled trial of sequential bilateral repetitive transcranial magnetic stimulation for treatment-resistant depression. *Am J Psychiatry*. 2006 Jan;163(1):88-94.
364. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, De Castella A, Kulkarni J. Transcranial magnetic stimulation in the treatment of depression: a double-blind, placebo-controlled trial. *Arch Gen Psychiatry*. 2003 Oct;60(10):1002-8.
365. Fitzgerald PB, Hoy K, McQueen S, Herring S, Segrave R, Been G, et al. Priming stimulation enhances the effectiveness of low-frequency right prefrontal cortex transcranial magnetic stimulation in major depression. *J Clin Psychopharmacol*. 2008 Feb;28(1):52-8.
366. Fitzgerald PB, Hoy K, McQueen S, Maller JJ, Herring S, Segrave R, et al. A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*. 2009 Apr;34(5):1255-62.

367. Fitzgerald PB, Huntsman S, Gunewardene R, Kulkarni J, Daskalakis ZJ. A randomized trial of low-frequency right-prefrontal-cortex transcranial magnetic stimulation as augmentation in treatment-resistant major depression. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):655-66.
368. Fitzgerald PB, McQueen S, Herring S, Hoy K, Segrave R, Kulkarni J, et al. A study of the effectiveness of high-frequency left prefrontal cortex transcranial magnetic stimulation in major depression in patients who have not responded to right-sided stimulation. *Psychiatry Res*. 2009 Aug 30;169(1):12-5.
369. Fitzgerald PB, Sritharan A, Daskalakis ZJ, de Castella AR, Kulkarni J, Egan G. A functional magnetic resonance imaging study of the effects of low frequency right prefrontal transcranial magnetic stimulation in depression. *J Clin Psychopharmacol*. 2007 Oct;27(5):488-92.
370. Fleck MP, Horwath E. Pharmacologic management of difficult-to-treat depression in clinical practice. *Psychiatr Serv*. 2005 Aug;56(8):1005-11.
371. Flint AJ, Rifat SL. A prospective study of lithium augmentation in antidepressant-resistant geriatric depression. *J Clin Psychopharmacol*. 1994 Oct;14(5):353-6.
372. Flint AJ, Rifat SL. The effect of sequential antidepressant treatment on geriatric depression. *J Affect Disord*. 1996 Jan 22;36(3-4):95-105.
373. Flint AJ, Rifat SL. Anxious depression in elderly patients. Response to antidepressant treatment. *Am J Geriatr Psychiatry*. 1997 Spring;5(2):107-15.
374. Flint AJ, Rifat SL. Effect of demographic and clinical variables on time to antidepressant response in geriatric depression. *Depress Anxiety*. 1997;5(2):103-7.
375. Flint AJ, Rifat SL. The treatment of psychotic depression in later life: a comparison of pharmacotherapy and ECT. *Int J Geriatr Psychiatry*. 1998 Jan;13(1):23-8.
376. Flint AJ, Rifat SL. Two-year outcome of psychotic depression in late life. *Am J Psychiatry*. 1998 Feb;155(2):178-83.
377. Flint AJ, Rifat SL. Maintenance treatment for recurrent depression in late life. A four-year outcome study. *Am J Geriatr Psychiatry*. 2000 Spring;8(2):112-6.
378. Flint AJ, Rifat SL. Nonresponse to first-line pharmacotherapy may predict relapse and recurrence of remitted geriatric depression. *Depress Anxiety*. 2001;13(3):125-31.
379. Folkerts HW, Michael N, Tölle R, Schonauer K, Mucke S, Schulze-Monking H. Electroconvulsive therapy vs. paroxetine in treatment-resistant depression -- a randomized study. *Acta Psychiatr Scand*. 1997 Nov;96(5):334-42.
380. Fontaine R, Ontiveros A, Elie R, Vezina M. Lithium carbonate augmentation of desipramine and fluoxetine in refractory depression. *Biol Psychiatry*. 1991 May 1;29(9):946-8.
381. Fontaine R, Young T. Unilateral ECT: advantages and efficacy in the treatment of depression. *Can J Psychiatry*. 1985 Mar;30(2):142-7.
382. Fountoulakis KN, Kantartzis S, Siamouli M, Panagiotidis P, Kaprinis S, Iacovides A, et al. Peripheral thyroid dysfunction in depression. *World J Biol Psychiatry*. 2006;7(3):131-7.
383. Franco-Bronson K. The management of treatment-resistant depression in the medically ill. *Psychiatr Clin North Am*. 1996 Jun;19(2):329-50.
384. Frasca TA, Iodice A, McCall WV. The relationship between changes in learning and memory after right unilateral electroconvulsive therapy. *J Ect*. 2003 Sep;19(3):148-50.
385. Fraser RM, Glass IB. Unilateral and bilateral ECT in elderly patients. A comparative study. *Acta Psychiatr Scand*. 1980 Jul;62(1):13-31.
386. Frederiksen SO, d'Elia G, Holsten F. Influence of ACTH 4-10 and unilateral ECT on primary and secondary memory in depressive patients. *Eur Arch Psychiatry Neurol Sci*. 1985;234(5):291-4.

387. Fredman B, d'Etienne J, Smith I, Husain MM, White PF. Anesthesia for electroconvulsive therapy: effects of propofol and methohexital on seizure activity and recovery. *Anesth Analg*. 1994 Jul;79(1):75-9.
388. Fredman SJ, Rosenbaum JF. Recurrent depression, resistant clinician? *Harv Rev Psychiatry*. 1998 Jan-Feb;5(5):281-5.
389. Freeman CP, Weeks D, Kendell RE. ECT: II: patients who complain. *Br J Psychiatry*. 1980 Jul;137:17-25.
390. Fregni F, Marcolin MA, Myczkowski M, Amiaz R, Hasey G, Rumi DO, et al. Predictors of antidepressant response in clinical trials of transcranial magnetic stimulation. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):641-54.
391. Fregni F, Ono CR, Santos CM, Bermpohl F, Buchpiguel C, Barbosa ER, et al. Effects of antidepressant treatment with rTMS and fluoxetine on brain perfusion in PD. *Neurology*. 2006 Jun 13;66(11):1629-37.
392. Fregni F, Santos CM, Myczkowski ML, Rigolino R, Gallucci-Neto J, Barbosa ER, et al. Repetitive transcranial magnetic stimulation is as effective as fluoxetine in the treatment of depression in patients with Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2004 Aug;75(8):1171-4.
393. Frith CD, Stevens M, Johnstone EC, Deakin JF, Lawler P, Crow TJ. Effects of ECT and depression on various aspects of memory. *Br J Psychiatry* 1983:610-7.
394. Frith CD, Stevens M, Johnstone EC, Deakin JF, Lawler P, Crow TJ. A comparison of some retrograde and anterograde effects of electroconvulsive shock in patients with severe depression. *Br J Psychol* 1987:53-63.
395. Frye MA, Ketter TA, Leverich GS, Huggins T, Lantz C, Denicoff KD, et al. The increasing use of polypharmacotherapy for refractory mood disorders: 22 years of study. *J Clin Psychiatry*. 2000 Jan;61(1):9-15.
396. Frye MA, Tsai GE, Huggins T, Coyle JT, Post RM. Low cerebrospinal fluid glutamate and glycine in refractory affective disorder. *Biol Psychiatry*. 2007 Jan 15;61(2):162-6.
397. Fu W, White PF. Dexmedetomidine failed to block the acute hyperdynamic response to electroconvulsive therapy. *Anesthesiology*. 1999 Feb;90(2):422-4.
398. Fujikawa T, Yokota N, Muraoka M, Yamawaki S. Response of patients with major depression and silent cerebral infarction to antidepressant drug therapy, with emphasis on central nervous system adverse reactions. *Stroke*. 1996 Nov;27(11):2040-2.
399. Fujita A, Nakaaki S, Segawa K, Azuma H, Sato K, Arahata K, et al. Memory, attention, and executive functions before and after sine and pulse wave electroconvulsive therapies for treatment-resistant major depression. *J Ect*. 2006 Jun;22(2):107-12.
400. Fulton B, Benfield P. Moclobemide. An update of its pharmacological properties and therapeutic use. *Drugs*. 1996 Sep;52(3):450-74.
401. Furtado CP, Maller JJ, Fitzgerald PB. A magnetic resonance imaging study of the entorhinal cortex in treatment-resistant depression. *Psychiatry Res*. 2008 Jul 15;163(2):133-42.
402. Gabriel A. Lamotrigine adjunctive treatment in resistant unipolar depression: an open, descriptive study. *Depress Anxiety*. 2006;23(8):485-8.
403. Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Praveen J, Reddy AK. Twice versus thrice weekly ECT in melancholia: a double-blind prospective comparison. *J Affect Disord*. 1993 Apr;27(4):273-8.
404. Gangadhar BN, Kapur RL, Kalyanasundaram S. Comparison of electroconvulsive therapy with imipramine in endogenous depression: a double blind study. *Br J Psychiatry*. 1982 Oct;141:367-71.
405. Gangadhar BN, Subbakrishna DK, Janakiramaiah N, Motreja S, Narayana Dutt D, Paramehwara G. Post-seizure EEG fractal dimension of first ECT predicts antidepressant response at two weeks. *J Affect Disord*. 1999 Jan-Mar;52(1-3):235-8.

406. Garcia-Toro M, Salva J, Daumal J, Andres J, Romera M, Lafau O, et al. High (20-Hz) and low (1-Hz) frequency transcranial magnetic stimulation as adjuvant treatment in medication-resistant depression. *Psychiatry Res.* 2006 Jan 30;146(1):53-7.
407. Garcia-Toro M, Segura C, Gonzalez A, Perello J, Valdivia J, Salazar R, et al. Inefficacy of burst-suppression anesthesia in medication-resistant major depression: a controlled trial. *J Ect.* 2001 Dec;17(4):284-8.
408. Gareri P, Falconi U, De Fazio P, De Sarro G. Conventional and new antidepressant drugs in the elderly. *Prog Neurobiol.* 2000 Jul;61(4):353-96.
409. Gareri P, Stilo G, Bevacqua I, Mattace R, Ferreri G, De Sarro G. Antidepressant drugs in the elderly. *Gen Pharmacol.* 1998 Apr;30(4):465-75.
410. Gastpar M. Clinical originality and new biology of trimipramine. *Drugs.* 1989;38 Suppl 1:43-8; discussion 9-50.
411. Gaszner P, Miklya I. The use of the synthetic enhancer substances (-)-deprenyl and (-)-BPAP in major depression. *Neuropsychopharmacol Hung.* 2004 Dec;6(4):210-20.
412. Gaszner P, Miklya I. Major depression and the synthetic enhancer substances, (-)-deprenyl and R-(-)-1-(benzofuran-2-yl)-2-propylaminopentane. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006 Jan;30(1):5-14.
413. Gaynes BN. Identifying difficult-to-treat depression: differential diagnosis, subtypes, and comorbidities. *J Clin Psychiatry.* 2009;70 Suppl 6:10-5.
414. Gaynes BN, Rush AJ, Trivedi MH, Wisniewski SR, Spencer D, Fava M. The STAR*D study: treating depression in the real world. *Cleve Clin J Med.* 2008 Jan;75(1):57-66.
415. Gebretsadik M, Jayaprabhu S, Grossberg GT. Mood disorders in the elderly. *Med Clin North Am.* 2006 Sep;90(5):789-805.
416. Geddes J, Butler R. Depressive disorders. *Clin Evid.* 2002 Jun(7):867-82.
417. Gelenberg AJ, Shelton RC, Crits-Christoph P, Keller MB, Dunner DL, Hirschfeld RM, et al. The effectiveness of St. John's Wort in major depressive disorder: a naturalistic phase 2 follow-up in which nonresponders were provided alternate medication. *J Clin Psychiatry.* 2004 Aug;65(8):1114-9.
418. Gelzer J. Limits to chemotherapy of depression. *Psychopathology.* 1986;19 Suppl 2:108-17.
419. George MS, Lisanby SH, Avery D, McDonald WM, Durkalski V, Pavlicova M, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry.* 2010/05/05 ed 2010:507-16.
420. George MS, Wassermann EM, Kimbrell TA, Little JT, Williams WE, Danielson AL, et al. Mood improvement following daily left prefrontal repetitive transcranial magnetic stimulation in patients with depression: a placebo-controlled crossover trial. *Am J Psychiatry.* 1997 Dec;154(12):1752-6.
421. Georgotas A, Friedman E, McCarthy M, Mann J, Krakowski M, Siegel R, et al. Resistant geriatric depressions and therapeutic response to monoamine oxidase inhibitors. *Biol Psychiatry.* 1983 Feb;18(2):195-205.
422. Geretsegger C, Nickel M, Judendorfer B, Rochowanski E, Novak E, Aichhorn W. Propofol and methohexital as anesthetic agents for electroconvulsive therapy: a randomized, double-blind comparison of electroconvulsive therapy seizure quality, therapeutic efficacy, and cognitive performance. *J Ect.* 2007 Dec;23(4):239-43.
423. Geretsegger C, Rochowanski E, Kartnig C, Unterrainer AF. Propofol and methohexital as anesthetic agents for electroconvulsive therapy (ECT): a comparison of seizure-quality measures and vital signs. *J Ect.* 1998 Mar;14(1):28-35.
424. Gershon AA, Dannon PN, Grunhaus L. Transcranial magnetic stimulation in the treatment of depression. *Am J Psychiatry.* 2003 May;160(5):835-45.
425. Gershon S. Chronic pain: hypothesized mechanism and rationale for treatment. *Neuropsychobiology.* 1986;15 Suppl 1:22-7.

426. Gervasoni N, Aubry JM, Gex-Fabry M, Bertschy G, Bondolfi G. Is there a place for tricyclic antidepressants and subsequent augmentation strategies in obtaining remission for patients with treatment resistant depression? *Pharmacol Res.* 2009 Mar;59(3):202-6.
427. Ghadirian AM, Murphy BE, Gendron MJ. Efficacy of light versus tryptophan therapy in seasonal affective disorder. *J Affect Disord.* 1998 Jul;50(1):23-7.
428. Ghaeli P, Shahsavand E, Mesbahi M, Kamkar MZ, Sadeghi M, Dashti-Khavidaki S. Comparing the effects of 8-week treatment with fluoxetine and imipramine on fasting blood glucose of patients with major depressive disorder. *J Clin Psychopharmacol.* 2004 Aug;24(4):386-8.
429. Ghaemi SN. Why antidepressants are not antidepressants: STEP-BD, STAR*D, and the return of neurotic depression. *Bipolar Disord.* 2008 Dec;10(8):957-68.
430. Giacobbe P, Mayberg HS, Lozano AM. Treatment resistant depression as a failure of brain homeostatic mechanisms: implications for deep brain stimulation. *Exp Neurol.* 2009 Sep;219(1):44-52.
431. Gilliam FG, Santos J, Vahle V, Carter J, Brown K, Hecimovic H. Depression in epilepsy: ignoring clinical expression of neuronal network dysfunction? *Epilepsia.* 2004;45 Suppl 2:28-33.
432. Gillin JC, Smith-Vaniz A, Schnierow B, Rapaport MH, Kelsoe J, Raimo E, et al. An open-label, 12-week clinical and sleep EEG study of nefazodone in chronic combat-related posttraumatic stress disorder. *J Clin Psychiatry.* 2001 Oct;62(10):789-96.
433. Gilmer WS, Gollan JK, Wisniewski SR, Howland RH, Trivedi MH, Miyahara S, et al. Does the duration of index episode affect the treatment outcome of major depressive disorder? A STAR*D report. *J Clin Psychiatry.* 2008 Aug;69(8):1246-56.
434. Gitlin MJ. Treatment-resistant depression. *West J Med.* 1991 Nov;155(5):521.
435. Gitlin MJ, Weiner H, Fairbanks L, Hershman JM, Friedfeld N. Failure of T3 to potentiate tricyclic antidepressant response. *J Affect Disord.* 1987 Nov-Dec;13(3):267-72.
436. Glassman AH. Antidepressant plasma levels revisited. *Int Clin Psychopharmacol.* 1994 Jun;9 Suppl 2:25-30.
437. Glover DS, Brown GP, Fairburn CG, Shafran R. A preliminary evaluation of cognitive-behaviour therapy for clinical perfectionism: a case series. *Br J Clin Psychol.* 2007 Mar;46(Pt 1):85-94.
438. Goff DC, Brotman AW, Waites M, McCormick S. Trial of fluoxetine added to neuroleptics for treatment-resistant schizophrenic patients. *Am J Psychiatry.* 1990 Apr;147(4):492-4.
439. Goff DC, Jenike MA. Treatment-resistant depression in the elderly. *J Am Geriatr Soc.* 1986 Jan;34(1):63-70.
440. Goldberg JF. The modern pharmacopoeia: a return to depressive realism? *Bipolar Disord.* 2008 Dec;10(8):969-72.
441. Gonzalez-Pinto A, Gutierrez M, Gonzalez N, Elizagarate E, Perez de Heredia JL, Mico JA. Efficacy and safety of venlafaxine-ECT combination in treatment-resistant depression. *J Neuropsychiatry Clin Neurosci.* 2002 Spring;14(2):206-9.
442. Goodman WK. Obsessive-compulsive disorder: diagnosis and treatment. *J Clin Psychiatry.* 1999;60 Suppl 18:27-32.
443. Goodman WK, McDougle CJ, Price LH. Pharmacotherapy of obsessive compulsive disorder. *J Clin Psychiatry.* 1992 Apr;53 Suppl:29-37.
444. Goodnick PJ, Sandoval R, Brickman A, Klimas NG. Bupropion treatment of fluoxetine-resistant chronic fatigue syndrome. *Biol Psychiatry.* 1992 Nov 1;32(9):834-8.
445. Gossen D, de Suray JM, Vandenhende F, Onkelinx C, Gangji D. Influence of fluoxetine on olanzapine pharmacokinetics. *AAPS PharmSci.* 2002;4(2):E11.
446. Goyal N, Nizamie SH, Desarkar P. Efficacy of adjuvant high frequency repetitive transcranial magnetic stimulation on negative and positive symptoms of schizophrenia: preliminary results of a double-blind sham-controlled study. *J Neuropsychiatry Clin Neurosci.* 2007 Fall;19(4):464-7.

447. Gram LF. Inadequate dosing and pharmacokinetic variability as confounding factors in assessment of efficacy of antidepressants. *Clin Neuropharmacol.* 1990;13 Suppl 1:S35-44.
448. Gram LF. Acute and continuation therapy in unipolar depression: observations from the run-in phase of a maintenance trial. *Acta Psychiatr Scand.* 2008 Aug;118(2):123-9.
449. Gran L, Bergsholm P, Bleie H. Seizure duration in unilateral electroconvulsive therapy. A comparison of the anaesthetic agents etomidate and Althesin with methohexitone. *Acta Psychiatr Scand.* 1984 Jun;69(6):472-83.
450. Graziottin A, Serafini A. Depression and the menopause: why antidepressants are not enough? *Menopause Int.* 2009 Jun;15(2):76-81.
451. Greden JF, Pande AC. Treatment of resistant depression with 5-HT uptake inhibitors. *Clin Neuropharmacol.* 1992;15 Suppl 1 Pt A:442A-3A.
452. Greenberg BD, Askland KD, Carpenter LL. The evolution of deep brain stimulation for neuropsychiatric disorders. *Front Biosci.* 2008;13:4638-48.
453. Greenberg P, Corey-Lisle PK, Birnbaum H, Marynchenko M, Claxton A. Economic implications of treatment-resistant depression among employees. *Pharmacoeconomics.* 2004;22(6):363-73.
454. Greenhalgh J, Knight C, Hind D, Beverley C, Walters S. Clinical and cost-effectiveness of electroconvulsive therapy for depressive illness, schizophrenia, catatonia and mania: systematic reviews and economic modelling studies. *Health Technol Assess.* 2005 Mar;9(9):1-156, iii-iv.
455. Greenlee BA, Ferrell RB, Kauffman CI, McAllister TW. Complex partial seizures and depression. *Curr Psychiatry Rep.* 2003 Oct;5(5):410-6.
456. Gregoire AJ, Kumar R, Everitt B, Henderson AF, Studd JW. Transdermal oestrogen for treatment of severe postnatal depression. *Lancet.* 1996 Apr 6;347(9006):930-3.
457. Grisaru N, Amir M, Cohen H, Kaplan Z. Effect of transcranial magnetic stimulation in posttraumatic stress disorder: a preliminary study. *Biol Psychiatry.* 1998 Jul 1;44(1):52-5.
458. Grisaru N, Chudakov B, Yaroslavsky Y, Belmaker RH. Transcranial magnetic stimulation in mania: a controlled study. *Am J Psychiatry.* 1998 Nov;155(11):1608-10.
459. Griskova I, Ruksenas O, Dapsys K, Herpertz S, Hoppner J. The effects of 10 Hz repetitive transcranial magnetic stimulation on resting EEG power spectrum in healthy subjects. *Neurosci Lett.* 2007 May 29;419(2):162-7.
460. Grof P, Joffe R, Kennedy S, Persad E, Syrotiuk J, Bradford D. An open study of oral flesinoxan, a 5-HT1A receptor agonist, in treatment-resistant depression. *Int Clin Psychopharmacol.* 1993 Fall;8(3):167-72.
461. Grote NK, Frank E. Difficult-to-treat depression: the role of contexts and comorbidities. *Biol Psychiatry.* 2003 Apr 15;53(8):660-70.
462. Gruber AJ, Hudson JI, Pope HG, Jr. The management of treatment-resistant depression in disorders on the interface of psychiatry and medicine. Fibromyalgia, chronic fatigue syndrome, migraine, irritable bowel syndrome, atypical facial pain, and premenstrual dysphoric disorder. *Psychiatr Clin North Am.* 1996 Jun;19(2):351-69.
463. Grunhaus L, Hirschman S, Dolberg OT, Schreiber S, Dannon PN. Coadministration of melatonin and fluoxetine does not improve the 3-month outcome following ECT. *J Ect.* 2001 Jun;17(2):124-8.
464. Grunhaus L, Polak D, Amiaz R, Dannon PN. Motor-evoked potential amplitudes elicited by transcranial magnetic stimulation do not differentiate between patients and normal controls. *Int J Neuropsychopharmacol.* 2003 Dec;6(4):371-8.
465. Grunhaus L, Schreiber S, Dolberg OT, Hirshman S, Dannon PN. Response to ECT in major depression: are there differences between unipolar and bipolar depression? *Bipolar Disord.* 2002;4 Suppl 1:91-3.

466. Grunhaus L, Shipley JE, Eiser A, Pande AC, Tandon R, Remen A, et al. Shortened REM latency PostECT is associated with rapid recurrence of depressive symptomatology. *Biol Psychiatry*. 1994 Aug 15;36(4):214-22.
467. Grunhaus L, Shipley JE, Eiser A, Pande AC, Tandon R, Remen A, et al. Polysomnographic studies in patients referred for ECT: pre-ECT studies. *Convuls Ther*. 1996 Dec;12(4):224-31.
468. Guscott R, Grof P. The clinical meaning of refractory depression: a review for the clinician. *Am J Psychiatry*. 1991 Jun;148(6):695-704.
469. Gutierrez MA, Stimmel GL, Aiso JY. Venlafaxine: a 2003 update. *Clin Ther*. 2003 Aug;25(8):2138-54.
470. Gutierrez RL, McKercher RM, Galea J, Jamison KL. Lamotrigine augmentation strategy for patients with treatment-resistant depression. *CNS Spectr*. 2005 Oct;10(10):800-5.
471. Haag S, Senf W, Tagay S, Langkafel M, Braun-Lang U, Pietsch A, et al. Is there a benefit from intensified medical and psychological interventions in patients with functional dyspepsia not responding to conventional therapy? *Aliment Pharmacol Ther*. 2007 Apr 15;25(8):973-86.
472. Hajak G, Marienhagen J, Langguth B, Werner S, Binder H, Eichhammer P. High-frequency repetitive transcranial magnetic stimulation in schizophrenia: a combined treatment and neuroimaging study. *Psychol Med*. 2004 Oct;34(7):1157-63.
473. Hallam KT, Smith DI, Berk M. Differences between subjective and objective assessments of the utility of Electroconvulsive therapy in patients with bipolar and unipolar depression. *J Affect Disord*. 2009 Jan;112(1-3):212-8.
474. Hamilton M. The effect of treatment on the melancholias (depressions). *Br J Psychiatry*. 1982 Mar;140:223-30.
475. Hanaoka N, Aoyama Y, Kameyama M, Fukuda M, Mikuni M. Deactivation and activation of left frontal lobe during and after low-frequency repetitive transcranial magnetic stimulation over right prefrontal cortex: a near-infrared spectroscopy study. *Neurosci Lett*. 2007 Mar 6;414(2):99-104.
476. Hansen PE, Videbech P, Clemmensen K, Sturlason R, Jensen HM, Vestergaard P. Repetitive transcranial magnetic stimulation as add-on antidepressant treatment. The applicability of the method in a clinical setting. *Nord J Psychiatry*. 2004;58(6):455-7.
477. Hantouche EG, Akiskal HS, Lancrenon S, Chatenet-Duchene L. Mood stabilizer augmentation in apparently "unipolar" MDD: predictors of response in the naturalistic French national EPIDEP study. *J Affect Disord*. 2005 Feb;84(2-3):243-9.
478. Harden CL. The co-morbidity of depression and epilepsy: epidemiology, etiology, and treatment. *Neurology*. 2002 Sep 24;59(6 Suppl 4):S48-55.
479. Hardy BG, Shulman KI, Zucchero C. Gradual discontinuation of lithium augmentation in elderly patients with unipolar depression. *J Clin Psychopharmacol*. 1997 Feb;17(1):22-6.
480. Harley R, Sprich S, Safren S, Jacobo M, Fava M. Adaptation of dialectical behavior therapy skills training group for treatment-resistant depression. *J Nerv Ment Dis*. 2008 Feb;196(2):136-43.
481. Harrison CL, Ferrier N, Young AH. Tolerability of high-dose venlafaxine in depressed patients. *J Psychopharmacol*. 2004 Jun;18(2):200-4.
482. Hartmann PM. Strategies for managing depression complicated by bipolar disorder, suicidal ideation, or psychotic features. *J Am Board Fam Pract*. 1996 Jul-Aug;9(4):261-9.
483. Hawley CJ, Quick SJ, Ratnam S, Pattinson HA, McPhee S. Safety and tolerability of combined treatment with moclobemide and SSRIs: a systematic study of 50 patients. *Int Clin Psychopharmacol*. 1996 Sep;11(3):187-91.
484. Hawley CJ, Roberts AG, Baldwin DS. Tolerability of combined treatment with lithium and fluoxetine: 14 cases treated under open conditions. *Int Clin Psychopharmacol*. 1994 Spring;9(1):31-3.

485. Healey WV, Khan A, Noonan C. Major depression with psychosis: demographic, phenomenological, and outcome characteristics in one hospitalized population. *J Nerv Ment Dis.* 1990 Nov;178(11):722-3.
486. Healy D, O'Halloran A, Carney PA, Leonard BE. Variations in platelet 5-hydroxytryptamine in control and depressed populations. *J Psychiatr Res.* 1986;20(4):345-53.
487. Healy D, Theodorou AE, Whitehouse AM, Lawrence KM, White W, Wilton-Cox H, et al. 3H-imipramine binding to previously frozen platelet membranes from depressed patients, before and after treatment. *Br J Psychiatry.* 1990 Aug;157:208-15.
488. Heijnen WT, van den Broek WW, Birkenhager TK. Treatment failure with a tricyclic antidepressant followed by lithium addition and response to subsequent electroconvulsive therapy. *J Clin Psychiatry.* 2008 Dec;69(12):1887-91.
489. Heikman P, Kalska H, Katila H, Sarna S, Tuunainen A, Kuoppasalmi K. Right unilateral and bifrontal electroconvulsive therapy in the treatment of depression: a preliminary study. *J Ect.* 2002 Mar;18(1):26-30.
490. Heikman P, Katila H, Sarna S, Wahlbeck K, Kuoppasalmi K. Differential response to right unilateral ECT in depressed patients: impact of comorbidity and severity of illness [ISRCTN39974945]. *BMC Psychiatry.* 2002;2:2.
491. Heikman P, Tuunainen A, Kuoppasalmi K. Value of the initial stimulus dose in right unilateral and bifrontal electroconvulsive therapy. *Psychol Med.* 1999 Nov;29(6):1417-23.
492. Heit S, Nemeroff CB. Lithium augmentation of antidepressants in treatment-refractory depression. *J Clin Psychiatry.* 1998;59 Suppl 6:28-33; discussion 4.
493. Heldt E, Manfro GG, Kipper L, Blaya C, Maltz S, Isolan L, et al. Treating medication-resistant panic disorder: predictors and outcome of cognitive-behavior therapy in a Brazilian public hospital. *Psychother Psychosom.* 2003 Jan-Feb;72(1):43-8.
494. Heninger GR, Charney DS, Sternberg DE. Lithium carbonate augmentation of antidepressant treatment. An effective prescription for treatment-refractory depression. *Arch Gen Psychiatry.* 1983 Dec;40(12):1335-42.
495. Henry ME, Schmidt ME, Matochik JA, Stoddard EP, Potter WZ. The effects of ECT on brain glucose: a pilot FDG PET study. *J Ect.* 2001 Mar;17(1):33-40.
496. Herbsman T, Avery D, Ramsey D, Holtzheimer P, Wadjik C, Hardaway F, et al. More lateral and anterior prefrontal coil location is associated with better repetitive transcranial magnetic stimulation antidepressant response. *Biol Psychiatry.* 2009/06/24 ed 2009:509-15.
497. Heresco-Levy U, Javitt DC, Gelfin Y, Gorelik E, Bar M, Blararu M, et al. Controlled trial of D-cycloserine adjuvant therapy for treatment-resistant major depressive disorder. *J Affect Disord.* 2006 Jul;93(1-3):239-43.
498. Hermesh H, Aizenberg D, Munitz H. Trazodone treatment in clomipramine-resistant obsessive-compulsive disorder. *Clin Neuropharmacol.* 1990 Aug;13(4):322-8.
499. Herr BE, Abraham HD, Anderson W. Length of stay in a general hospital psychiatric unit. *Gen Hosp Psychiatry.* 1991 Jan;13(1):68-70.
500. Herwig U, Cardenas-Morales L, Connemann BJ, Kammer T, Schonfeldt-Lecuona C. Sham or real--post hoc estimation of stimulation condition in a randomized transcranial magnetic stimulation trial. *Neurosci Lett.* 2010 Feb 26;471(1):30-3.
501. Herwig U, Fallgatter AJ, Hoppner J, Eschweiler GW, Kron M, Hajak G, et al. Antidepressant effects of augmentative transcranial magnetic stimulation: randomised multicentre trial. *Br J Psychiatry.* 2007 Nov;191:441-8.
502. Herwig U, Padberg F, Unger J, Spitzer M, Schonfeldt-Lecuona C. Transcranial magnetic stimulation in therapy studies: examination of the reliability of "standard" coil positioning by neuronavigation. *Biol Psychiatry.* 2001 Jul 1;50(1):58-61.

503. Hickie I, Bennett B, Mitchell P, Wilhelm K, Orlay W. Clinical and subclinical hypothyroidism in patients with chronic and treatment-resistant depression. *Aust N Z J Psychiatry*. 1996 Apr;30(2):246-52.
504. Hickie I, Mason C, Parker G. Comparative validity of two measures of psychomotor function in patients with severe depression. *J Affect Disord*. 1996 Apr 12;37(2-3):143-9.
505. Hickie I, Mason C, Parker G, Brodaty H. Prediction of ECT response: validation of a refined sign-based (CORE) system for defining melancholia. *Br J Psychiatry*. 1996 Jul;169(1):68-74.
506. Hill MN, Gorzalka BB. Is there a role for the endocannabinoid system in the etiology and treatment of melancholic depression? *Behav Pharmacol*. 2005 Sep;16(5-6):333-52.
507. Hirschfeld RM. Efficacy of SSRIs and newer antidepressants in severe depression: comparison with TCAs. *J Clin Psychiatry*. 1999 May;60(5):326-35.
508. Hirschfeld RM. The use of mirtazapine in difficult-to-treat patient populations. *Hum Psychopharmacol*. 2002 Jun;17 Suppl 1:S33-6.
509. Hirschfeld RM, Lewis L, Vornik LA. Perceptions and impact of bipolar disorder: how far have we really come? Results of the national depressive and manic-depressive association 2000 survey of individuals with bipolar disorder. *J Clin Psychiatry*. 2003 Feb;64(2):161-74.
510. Hoencamp E, Haffmans J, Dijken WA, Huijbrechts IP. Lithium augmentation of venlafaxine: an open-label trial. *J Clin Psychopharmacol*. 2000 Oct;20(5):538-43.
511. Hoepfner J, Padberg F, Domes G, Zinke A, Herpertz SC, Grossheinrich N, et al. Influence of repetitive transcranial magnetic stimulation on psychomotor symptoms in major depression. *Eur Arch Psychiatry Clin Neurosci*. 2010 Apr;260(3):197-202.
512. Hofmann P, Gangadhar BN, Probst C, Koinig G, Hatzinger R. TSH response to TRH and ECT. *J Affect Disord*. 1994 Oct;32(2):127-31.
513. Hoiriis KT, Pflieger B, McDuffie FC, Cotsonis G, Elsangak O, Hinson R, et al. A randomized clinical trial comparing chiropractic adjustments to muscle relaxants for subacute low back pain. *J Manipulative Physiol Ther*. 2004 Jul-Aug;27(6):388-98.
514. Holm KJ, Markham A. Mirtazapine: a review of its use in major depression. *Drugs*. 1999 Apr;57(4):607-31.
515. Holsboer F. Prediction of clinical course by dexamethasone suppression test (DST) response in depressed patients - physiological and clinical construct validity of the DST. *Pharmacopsychiatry*. 1983 Nov;16(6):186-91.
516. Holtzheimer PE, 3rd, Russo J, Claypoole KH, Roy-Byrne P, Avery DH. Shorter duration of depressive episode may predict response to repetitive transcranial magnetic stimulation. *Depress Anxiety*. 2004;19(1):24-30.
517. Holzer M, Padberg F. Intermittent theta burst stimulation (iTBS) ameliorates therapy-resistant depression: a case series. *Brain Stimul*. 2010 Jul;3(3):181-3.
518. Hong CJ, Wang YC, Tsai SJ. Association study of angiotensin I-converting enzyme polymorphism and symptomatology and antidepressant response in major depressive disorders. *J Neural Transm*. 2002 Sep;109(9):1209-14.
519. Honkonen TI, Aro TA, Isometsa ET, Virtanen EM, Katila HO. Quality of treatment and disability compensation in depression: comparison of 2 nationally representative samples with a 10-year interval in Finland. *J Clin Psychiatry*. 2007 Dec;68(12):1886-93.
520. Horne RL, Pettinati HM, Sugerma AA, Varga E. Comparing bilateral to unilateral electroconvulsive therapy in a randomized study with EEG monitoring. *Arch Gen Psychiatry*. 1985 Nov;42(11):1087-92.
521. Hornig M, Mozley PD, Amsterdam JD. HMPAO SPECT brain imaging in treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1997 Oct;21(7):1097-114.

522. Hornig-Rohan M, Wolkowitz OM, Amsterdam JD. Novel strategies for treatment-resistant depression. *Psychiatr Clin North Am.* 1996 Jun;19(2):387-405.
523. House A, Bostock J, Cooper J. Depressive syndromes in the year following onset of a first schizophrenic illness*. *Br J Psychiatry.* 1987 Dec;151:773-9.
524. Howland RH. Pharmacotherapy strategies for treatment-resistant depression. *J Psychosoc Nurs Ment Health Serv.* 2006 Nov;44(11):11-4.
525. Howland RH. Therapeutic armamentarium for treating depression. *Postgrad Med.* 2010 Jul;122(4):66-93.
526. Hsieh MH, McQuoid DR, Levy RM, Payne ME, MacFall JR, Steffens DC. Hippocampal volume and antidepressant response in geriatric depression. *Int J Geriatr Psychiatry.* 2002 Jun;17(6):519-25.
527. Huang CC, Su TP, Wei IH. Repetitive transcranial magnetic stimulation for treating medication-resistant depression in Taiwan: a preliminary study. *J Chin Med Assoc.* 2005 May;68(5):210-5.
528. Huang CC, Wei IH, Chou YH, Su TP. Effect of age, gender, menopausal status, and ovarian hormonal level on rTMS in treatment-resistant depression. *Psychoneuroendocrinology.* 2008 Jul;33(6):821-31.
529. Hung YY, Huang TL. Lorazepam and diazepam rapidly relieve catatonic features in major depression. *Clin Neuropharmacol.* 2006 May-Jun;29(3):144-7.
530. Husain MM, McClintock SM, Rush AJ, Knapp RG, Fink M, Rummans TA, et al. The efficacy of acute electroconvulsive therapy in atypical depression. *J Clin Psychiatry.* 2008 Mar;69(3):406-11.
531. Husain MM, Rush AJ, Fink M, Knapp R, Petrides G, Rummans T, et al. Speed of response and remission in major depressive disorder with acute electroconvulsive therapy (ECT): a Consortium for Research in ECT (CORE) report. *J Clin Psychiatry.* 2004 Apr;65(4):485-91.
532. Husain SS, Kevan IM, Linnell R, Scott AI. Electroconvulsive therapy in depressive illness that has not responded to drug treatment. *J Affect Disord.* 2004 Dec;83(2-3):121-6.
533. Husain SS, Kevan IM, Linnell R, Scott AI. What do psychiatrists mean by medication resistance as an indication for electroconvulsive therapy? *J Ect.* 2005 Dec;21(4):211-3.
534. Huuhka K, Kampman O, Anttila S, Huuhka M, Rontu R, Mattila KM, et al. RGS4 polymorphism and response to electroconvulsive therapy in major depressive disorder. *Neurosci Lett.* 2008 May 23;437(1):25-8.
535. Huuhka M, Korpisammal L, Haataja R, Leinonen E. One-year outcome of elderly inpatients with major depressive disorder treated with ECT and antidepressants. *J Ect.* 2004 Sep;20(3):179-85.
536. Huuhka MJ, Haanpaa ML, Leinonen EV. Electroconvulsive therapy in patients with depression and fibromyalgia. *Eur J Pain.* 2004 Aug;8(4):371-6.
537. Ide M, Kadoi Y, Saito S, Takahashi K, Sawano Y, Miyazaki M, et al. Effects of landiolol on left ventricular function during electroconvulsive therapy: a transthoracic echocardiographic study. *J Anesth.* 2010 Apr;24(2):272-6.
538. Ikeji OC, Ohaeri JU, Osahon RO, Agidee RO. Naturalistic comparative study of outcome and cognitive effects of unmodified electro-convulsive therapy in schizophrenia, mania and severe depression in Nigeria. *East Afr Med J.* 1999 Nov;76(11):644-50.
539. Inglot AD, Leszek J, Piasecki E, Sypula A. Interferon responses in schizophrenia and major depressive disorders. *Biol Psychiatry.* 1994 Apr 1;35(7):464-73.
540. Ingram A, Schweitzer I, Ng CH, Saling MM, Savage G. A comparison of propofol and thiopentone use in electroconvulsive therapy: cognitive and efficacy effects. *J Ect.* 2007 Sep;23(3):158-62.

541. Inoue T, Nakagawa S, Kitaichi Y, Izumi T, Tanaka T, Masui T, et al. Long-term outcome of antidepressant-refractory depression: the relevance of unrecognized bipolarity. *J Affect Disord.* 2006 Oct;95(1-3):61-7.
542. Inoue T, Tsuchiya K, Miura J, Sakakibara S, Denda K, Kasahara T, et al. Bromocriptine treatment of tricyclic and heterocyclic antidepressant-resistant depression. *Biol Psychiatry.* 1996 Jul 15;40(2):151-3.
543. Isometsa ET, Henriksson MM, Aro HM, Heikkinen ME, Kuoppasalmi KI, Lonnqvist JK. Suicide in major depression. *Am J Psychiatry.* 1994 Apr;151(4):530-6.
544. Ivkovic M, Damjanovic A, Jovanovic A, Cvetic T, Jasovic-Gasic M. Lamotrigine versus lithium augmentation of antidepressant therapy in treatment-resistant depression: efficacy and tolerability. *Psychiatr Danub.* 2009 Jun;21(2):187-93.
545. Jagadeesh HN, Gangadhar BN, Janakiramaiah N, Subbakrishna DK, Jain S. Time dependent therapeutic effects of single electroconvulsive therapy (ECT) in endogenous depression. *J Affect Disord.* 1992 Apr;24(4):291-5.
546. Janakiramaiah N, Gangadhar BN, Naga Venkatesha Murthy PJ, Harish MG, Subbakrishna DK, Vedamurthachar A. Antidepressant efficacy of Sudarshan Kriya Yoga (SKY) in melancholia: a randomized comparison with electroconvulsive therapy (ECT) and imipramine. *J Affect Disord.* 2000 Jan-Mar;57(1-3):255-9.
547. Janicak PG, Dowd SM, Martis B, Alam D, Beedle D, Krasuski J, et al. Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial. *Biol Psychiatry.* 2002 Apr 15;51(8):659-67.
548. Janicak PG, Martis B. Strategies for treatment-resistant depression. *Clin Cornerstone.* 1999;1(4):58-71.
549. Janicak PG, O'Reardon JP, Sampson SM, Husain MM, Lisanby SH, Rado JT, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry.* 2008 Feb;69(2):222-32.
550. Janicak PG, Sharma RP, Israni TH, Dowd SM, Altman E, Davis JM. Effects of unilateral-nondominant vs. bilateral ECT on memory and depression: a preliminary report. *Psychopharmacol Bull.* 1991;27(3):353-7.
551. Jann MW, Slade JH. Antidepressant agents for the treatment of chronic pain and depression. *Pharmacotherapy.* 2007 Nov;27(11):1571-87.
552. Januel D, Dumortier G, Verdon CM, Stamatiadis L, Saba G, Cabaret W, et al. A double-blind sham controlled study of right prefrontal repetitive transcranial magnetic stimulation (rTMS): therapeutic and cognitive effect in medication free unipolar depression during 4 weeks. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006 Jan;30(1):126-30.
553. Januel D, Massot O, Poirier MF, Olie JP, Fillion G. Interaction of lithium with 5-HT(1B) receptors in depressed unipolar patients treated with clomipramine and lithium versus clomipramine and placebo: preliminary results. *Psychiatry Res.* 2002 Aug 30;111(2-3):117-24.
554. Januel D, Poirier MF, D'Alche-Biree F, Dib M, Olie JP. Multicenter double-blind randomized parallel-group clinical trial of efficacy of the combination clomipramine (150 mg/day) plus lithium carbonate (750 mg/day) versus clomipramine (150 mg/day) plus placebo in the treatment of unipolar major depression. *J Affect Disord.* 2003 Sep;76(1-3):191-200.
555. Jenike MA. Treatment of affective illness in the elderly with drugs and electroconvulsive therapy. *J Geriatr Psychiatry.* 1989;22(1):77-112; discussion 3-20.
556. Jenike MA. An update on obsessive-compulsive disorder. *Bull Menninger Clin.* 2001 Winter;65(1):4-25.

557. Jha A, Stein G. Decreased efficacy of combined benzodiazepines and unilateral ECT in treatment of depression. *Acta Psychiatr Scand*. 1996 Aug;94(2):101-4.
558. Joffe RT. Peripheral thyroid hormone levels in treatment resistant depression. *Biol Psychiatry*. 1999 Apr 15;45(8):1053-5.
559. Joffe RT, Bakish D. Combined SSRI-moclobemide treatment of psychiatric illness. *J Clin Psychiatry*. 1994 Jan;55(1):24-5.
560. Joffe RT, Levitt AJ, Sokolov ST. Augmentation strategies: focus on anxiolytics. *J Clin Psychiatry*. 1996;57 Suppl 7:25-31; discussion 2-3.
561. Joffe RT, Schuller DR. An open study of buspirone augmentation of serotonin reuptake inhibitors in refractory depression. *J Clin Psychiatry*. 1993 Jul;54(7):269-71.
562. Joffe RT, Singer W, Levitt AJ, MacDonald C. A placebo-controlled comparison of lithium and triiodothyronine augmentation of tricyclic antidepressants in unipolar refractory depression. *Arch Gen Psychiatry*. 1993 May;50(5):387-93.
563. Joffe RT, Sokolov ST, Levitt AJ. Lithium and triiodothyronine augmentation of antidepressants. *Can J Psychiatry*. 2006 Oct;51(12):791-3.
564. Joffe RT, Sokolov ST, Singer W. Thyroid hormone treatment of depression. *Thyroid*. 1995 Jun;5(3):235-9.
565. Johanson A, Gustafson L, Risberg J, Rosen I, Sjobeck M, Silfverskiold P. Long-term follow-up in depressed patients treated with electroconvulsive therapy. *J Ect*. 2005 Dec;21(4):214-20.
566. Johansson M, Ehnvall A, Friberg P, Myredal A. Arterial baroreflex dysfunction in major depressive disorder. *Clin Auton Res*. 2010 Aug;20(4):235-40.
567. Johnson GF. Lithium in depression: a review of the antidepressant and prophylactic effects of lithium. *Aust N Z J Psychiatry*. 1987 Sep;21(3):356-65.
568. Johnstone EC, Deakin JF, Lawler P, Frith CD, Stevens M, McPherson K, et al. The Northwick Park electroconvulsive therapy trial. *Lancet* 1980:1317-20.
569. Jorge RE, Moser DJ, Acion L, Robinson RG. Treatment of vascular depression using repetitive transcranial magnetic stimulation. *Arch Gen Psychiatry*. 2008 Mar;65(3):268-76.
570. Jorge RE, Robinson RG, O'Brien J. Top cited papers in international psychogeriatrics: 5. A controlled study of repetitive transcranial magnetic stimulation as a treatment of depression in the elderly. *Int Psychogeriatr*. 2009 Oct;21(5):855-60.
571. Jorge RE, Robinson RG, Tateno A, Narushima K, Acion L, Moser D, et al. Repetitive transcranial magnetic stimulation as treatment of poststroke depression: a preliminary study. *Biol Psychiatry*. 2004 Feb 15;55(4):398-405.
572. Joseph MH, Risby D, Crow TJ, Deakin JF, Johnstone EC, Lawler P. MHPG excretion in endogenous depression: relationship to clinical state and the effects of ECT. *Psychopharmacology (Berl)*. 1985;87(4):442-8.
573. Kahkonen S, Komssi S, Wilenius J, Ilmoniemi RJ. Prefrontal TMS produces smaller EEG responses than motor-cortex TMS: implications for rTMS treatment in depression. *Psychopharmacology (Berl)*. 2005 Aug;181(1):16-20.
574. Kalb R, Ellinger K, Reulbach U. Improvement in response times for simple and complex tasks after electroconvulsive therapy. *Prog Neuropsychopharmacol Biol Psychiatry*. 2003 May;27(3):459-65.
575. Kamholz BA, Mellow AM. Management of treatment resistance in the depressed geriatric patient. *Psychiatr Clin North Am*. 1996 Jun;19(2):269-86.
576. Kantor D, McNevin S, Leichner P, Harper D, Krenn M. The benefit of lithium carbonate adjunct in refractory depression--fact or fiction? *Can J Psychiatry*. 1986 Jun;31(5):416-8.
577. Kaplan R. Obstructive sleep apnoea and depression--diagnostic and treatment implications. *Aust N Z J Psychiatry*. 1992 Dec;26(4):586-91.

578. Karp JF, Whyte EM, Lenze EJ, Dew MA, Begley A, Miller MD, et al. Rescue pharmacotherapy with duloxetine for selective serotonin reuptake inhibitor nonresponders in late-life depression: outcome and tolerability. *J Clin Psychiatry*. 2008 Mar;69(3):457-63.
579. Kasper S. The rationale for long-term antidepressant therapy. *Int Clin Psychopharmacol*. 1993 Winter;8(4):225-35.
580. Kato M, Fukuda T, Serretti A, Wakeno M, Okugawa G, Ikenaga Y, et al. ABCB1 (MDR1) gene polymorphisms are associated with the clinical response to paroxetine in patients with major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008 Feb 15;32(2):398-404.
581. Katona CL. Puerperal mental illness: comparisons with non-puerperal controls. *Br J Psychiatry*. 1982 Nov;141:447-52.
582. Katona CL. Lithium augmentation in refractory depression. *Psychiatr Dev*. 1988 Summer;6(2):153-71.
583. Katona CL. Refractory depression: a review with particular reference to the use of lithium augmentation. *Eur Neuropsychopharmacol*. 1995;5 Suppl:109-13.
584. Katz MM, Koslow SH, Maas JW, Frazer A, Kocsis J, Secunda S, et al. Identifying the specific clinical actions of amitriptyline: interrelationships of behaviour, affect and plasma levels in depression. *Psychol Med*. 1991 Aug;21(3):599-611.
585. Kaymaz N, van Os J, Loonen AJ, Nolen WA. Evidence that patients with single versus recurrent depressive episodes are differentially sensitive to treatment discontinuation: a meta-analysis of placebo-controlled randomized trials. *J Clin Psychiatry*. 2008 Sep;69(9):1423-36.
586. Keeley R, Smith M, Miller J. Somatoform symptoms and treatment nonadherence in depressed family medicine outpatients. *Arch Fam Med*. 2000 Jan;9(1):46-54.
587. Keitner GI, Ryan CE, Solomon DA. Realistic expectations and a disease management model for depressed patients with persistent symptoms. *J Clin Psychiatry*. 2006 Sep;67(9):1412-21.
588. Keks NA, Burrows GD, Copolov DL, Newton R, Paoletti N, Schweitzer I, et al. Beyond the evidence: is there a place for antidepressant combinations in the pharmacotherapy of depression? *Med J Aust*. 2007 Feb 5;186(3):142-4.
589. Keller MB. Issues in treatment-resistant depression. *J Clin Psychiatry*. 2005;66 Suppl 8:5-12.
590. Keller MB, Shapiro RW. Major depressive disorder. Initial results from a one-year prospective naturalistic follow-up study. *J Nerv Ment Dis*. 1981 Dec;169(12):761-8.
591. Kellner CH, Husain M, Petrides G, Fink M, Rummans T. Comment on "Repetitive transcranial magnetic stimulation versus electroconvulsive therapy for major depression: preliminary results of a randomized trial". *Biol Psychiatry*. 2002 Nov 15;52(10):1032-3; discussion 3.
592. Kellner CH, Knapp R, Husain MM, Rasmussen K, Sampson S, Cullum M, et al. Bifrontal, bitemporal and right unilateral electrode placement in ECT: randomised trial. *Br J Psychiatry*. 2010 Mar;196:226-34.
593. Kellner CH, Knapp RG, Petrides G, Rummans TA, Husain MM, Rasmussen K, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 2006:1337-44.
594. Kelly TF, Lieberman DZ. Long term augmentation with T3 in refractory major depression. *J Affect Disord*. 2009 May;115(1-2):230-3.
595. Kelway B, Simpson KH, Smith RJ, Halsall PJ. Effects of atropine and glycopyrrolate on cognitive function following anaesthesia and electroconvulsive therapy (ECT). *Int Clin Psychopharmacol*. 1986 Oct;1(4):296-302.
596. Kennedy N, Paykel ES. Treatment and response in refractory depression: results from a specialist affective disorders service. *J Affect Disord*. 2004 Jul;81(1):49-53.
597. Kennedy SH, Joffe RT. Pharmacological management of refractory depression. *Can J Psychiatry*. 1989 Jun;34(5):451-6.

598. Kennedy SH, Lam RW, Cohen NL, Rosenbluth M, Sokolov ST, McIntyre RS, et al. Reboxetine: a preliminary report on its use through the Special Access Program. *J Psychiatry Neurosci.* 2002 Nov;27(6):418-22.
599. Kennedy SH, Milev R, Giacobbe P, Ramasubbu R, Lam RW, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) Clinical guidelines for the management of major depressive disorder in adults. IV. Neurostimulation therapies. *J Affect Disord.* 2009 Oct;117 Suppl 1:S44-53.
600. Ketter TA, Post RM, Parekh PI, Worthington K. Addition of monoamine oxidase inhibitors to carbamazepine: preliminary evidence of safety and antidepressant efficacy in treatment-resistant depression. *J Clin Psychiatry.* 1995 Oct;56(10):471-5.
601. Khalid N, Atkins M, Tredget J, Giles M, Champney-Smith K, Kirov G. The effectiveness of electroconvulsive therapy in treatment-resistant depression: a naturalistic study. *J Ect.* 2008 Jun;24(2):141-5.
602. Khan A, Johnson F, Avery DH, Cohen S, Scherzo B, Dunner DL. DST results in nonpsychotic depressed outpatients. *Am J Psychiatry.* 1988 Sep;145(9):1153-6.
603. Khan A, Mirolo MH, Claypoole K, Bhang J, Cox G, Horita A, et al. Effects of low-dose TRH on cognitive deficits in the ECT postictal state. *Am J Psychiatry.* 1994 Nov;151(11):1694-6.
604. Kielholz P. Treatment for therapy-resistant depression. *Psychopathology.* 1986;19 Suppl 2:194-200.
605. Kikuchi A, Yasui-Furukori N, Fujii A, Katagai H, Kaneko S. Identification of predictors of post-ictal delirium after electroconvulsive therapy. *Psychiatry Clin Neurosci.* 2009 Apr;63(2):180-5.
606. Kiloh LG. Non-pharmacological biological treatments of psychiatric patients. *Aust N Z J Psychiatry.* 1983 Sep;17(3):215-25.
607. Kimball JN, Rosenquist PB, Dunn A, McCall V. Prediction of antidepressant response in both 2.25xthreshold RUL and fixed high dose RUL ECT. *J Affect Disord.* 2009 Jan;112(1-3):85-91.
608. Kimbrell TA, Little JT, Dunn RT, Frye MA, Greenberg BD, Wassermann EM, et al. Frequency dependence of antidepressant response to left prefrontal repetitive transcranial magnetic stimulation (rTMS) as a function of baseline cerebral glucose metabolism. *Biol Psychiatry.* 1999 Dec 15;46(12):1603-13.
609. Kirchheiner J, Bertilsson L, Bruus H, Wolff A, Roots I, Bauer M. Individualized medicine - implementation of pharmacogenetic diagnostics in antidepressant drug treatment of major depressive disorders. *Pharmacopsychiatry.* 2003 Nov;36 Suppl 3:S235-43.
610. Kirkby KC, Beckett WG, Matters RM, King TE. Comparison of propofol and methohexitone in anaesthesia for ECT: effect on seizure duration and outcome. *Aust N Z J Psychiatry.* 1995 Jun;29(2):299-303.
611. Kirov G, Ebmeier KP, Scott AI, Atkins M, Khalid N, Carrick L, et al. Quick recovery of orientation after magnetic seizure therapy for major depressive disorder. *Br J Psychiatry.* 2008 Aug;193(2):152-5.
612. Kito S, Fujita K, Koga Y. Regional cerebral blood flow changes after low-frequency transcranial magnetic stimulation of the right dorsolateral prefrontal cortex in treatment-resistant depression. *Neuropsychobiology.* 2008;58(1):29-36.
613. Kito S, Fujita K, Koga Y. Changes in regional cerebral blood flow after repetitive transcranial magnetic stimulation of the left dorsolateral prefrontal cortex in treatment-resistant depression. *J Neuropsychiatry Clin Neurosci.* 2008 Winter;20(1):74-80.
614. Kito S, Hasegawa T, Fujita K, Koga Y. Changes in hypothalamic-pituitary-thyroid axis following successful treatment with low-frequency right prefrontal transcranial magnetic stimulation in treatment-resistant depression. *Psychiatry Res.* 2010 Jan 30;175(1-2):74-7.
615. Klein E, Kreinin I, Chistyakov A, Koren D, Mecz L, Marmur S, et al. Therapeutic efficacy of right prefrontal slow repetitive transcranial magnetic stimulation in major depression: a double-blind controlled study. *Arch Gen Psychiatry.* 1999 Apr;56(4):315-20.

616. Klein N, Sacher J, Wallner H, Tauscher J, Kasper S. Therapy of treatment resistant depression: focus on the management of TRD with atypical antipsychotics. *CNS Spectr*. 2004 Nov;9(11):823-32.
617. Kocsis JH, Frances A, Kalman TP, Shear MK. The effect of psychobiological research on treatment outcome. A controlled study. *Arch Gen Psychiatry*. 1981 May;38(5):511-5.
618. Koerselman F, Laman DM, van Duijn H, van Duijn MA, Willems MA. A 3-month, follow-up, randomized, placebo-controlled study of repetitive transcranial magnetic stimulation in depression. *J Clin Psychiatry*. 2004 Oct;65(10):1323-8.
619. Kohn R, Epstein-Lubow G. Course and outcomes of depression in the elderly. *Curr Psychiatry Rep*. 2006 Feb;8(1):34-40.
620. Kok RM, Vink D, Heeren TJ, Nolen WA. Lithium augmentation compared with phenelzine in treatment-resistant depression in the elderly: an open, randomized, controlled trial. *J Clin Psychiatry*. 2007 Aug;68(8):1177-85.
621. Konarski JZ, Kennedy SH, Segal ZV, Lau MA, Bieling PJ, McIntyre RS, et al. Predictors of nonresponse to cognitive behavioural therapy or venlafaxine using glucose metabolism in major depressive disorder. *J Psychiatry Neurosci*. 2009 May;34(3):175-80.
622. Kondziella D, Asztely F. Don't be afraid to treat depression in patients with epilepsy! *Acta Neurol Scand*. 2009 Feb;119(2):75-80.
623. Konig F, Wolfersdorf M. Combination therapy using moclobemide with tricyclic and tetracyclic antidepressants to treat therapy-resistant depression. *Pharmacopsychiatry*. 1997 May;30(3):93-6.
624. Konig F, Wolfersdorf M, Loble M, Wossner S, Hauger B. Trimipramine and maprotiline plasma levels during combined treatment with moclobemide in therapy-resistant depression. *Pharmacopsychiatry*. 1997 Jul;30(4):125-7.
625. Kopecek M, Cerna L, Sulak J, Raszka M, Bares M, Seifertova D. Depressed patients perception of the efficacy of electroconvulsive therapy and venlafaxine therapy. *Neuro Endocrinol Lett*. 2007 Dec;28(6):889-94.
626. Kopf D, Westphal S, Luley CW, Ritter S, Gilles M, Weber-Hamann B, et al. Lipid metabolism and insulin resistance in depressed patients: significance of weight, hypercortisolism, and antidepressant treatment. *J Clin Psychopharmacol*. 2004 Oct;24(5):527-31.
627. Kornbluh R, Papakostas GI, Petersen T, Neault NB, Nierenberg AA, Rosenbaum JF, et al. A survey of prescribing preferences in the treatment of refractory depression: recent trends. *Psychopharmacol Bull*. 2001 Summer;35(3):150-6.
628. Kornstein SG, Schneider RK. Clinical features of treatment-resistant depression. *J Clin Psychiatry*. 2001;62 Suppl 16:18-25.
629. Kostowski W. Recent advances in the GABA-A-benzodiazepine receptor pharmacology. *Pol J Pharmacol*. 1995 May-Jun;47(3):237-46.
630. Kotresh S, Girish K, Janakiramaiah N, Rao GU, Gangadhar BN. Effect of ECT stimulus parameters on seizure physiology and outcome. *J Ect*. 2004 Mar;20(1):10-2.
631. Kraft JB, Peters EJ, Slager SL, Jenkins GD, Reinalda MS, McGrath PJ, et al. Analysis of association between the serotonin transporter and antidepressant response in a large clinical sample. *Biol Psychiatry*. 2007 Mar 15;61(6):734-42.
632. Kral VA, Emery OB. Long-term follow-up of depressive pseudodementia of the aged. *Can J Psychiatry*. 1989 Jun;34(5):445-6.
633. Kramlinger KG, Post RM. The addition of lithium to carbamazepine. Antidepressant efficacy in treatment-resistant depression. *Arch Gen Psychiatry*. 1989 Sep;46(9):794-800.
634. Krisanaprakornkit T, Paholpak S, Tassaniyom K, Pimpanit V. Transcranial magnetic stimulation for treatment resistant depression: six case reports and review. *J Med Assoc Thai*. 2010 May;93(5):580-6.

635. Krog-Meyer I, Kirkegaard C, Kijne B, Lumholtz B, Smith E, Lykke-Olesen L, et al. Prediction of relapse with the TRH test and prophylactic amitriptyline in 39 patients with endogenous depression. *Am J Psychiatry*. 1984 Aug;141(8):945-8.
636. Krystal AD, Holsinger T, Weiner RD, Coffey CE. Prediction of the utility of a switch from unilateral to bilateral ECT in the elderly using treatment 2 ictal EEG indices. *J Ect*. 2000 Dec;16(4):327-37.
637. Krystal AD, Weiner RD, Gassert D, McCall WV, Coffey CE, Sibert T, et al. The relative ability of three ictal EEG frequency bands to differentiate ECT seizures on the basis of electrode placement, stimulus intensity, and therapeutic response. *Convuls Ther*. 1996 Mar;12(1):13-24.
638. Krystal AD, Weiner RD, McCall WV, Shelp FE, Arias R, Smith P. The effects of ECT stimulus dose and electrode placement on the ictal electroencephalogram: an intraindividual crossover study. *Biol Psychiatry*. 1993 Dec 1;34(11):759-67.
639. Kubera M, Kenis G, Bosmans E, Kajta M, Basta-Kaim A, Scharpe S, et al. Stimulatory effect of antidepressants on the production of IL-6. *Int Immunopharmacol*. 2004 Feb;4(2):185-92.
640. Kubera M, Lin AH, Kenis G, Bosmans E, van Bockstaele D, Maes M. Anti-inflammatory effects of antidepressants through suppression of the interferon-gamma/interleukin-10 production ratio. *J Clin Psychopharmacol*. 2001 Apr;21(2):199-206.
641. Kubera M, Van Bockstaele D, Maes M. Leukocyte subsets in treatment-resistant major depression. *Pol J Pharmacol*. 1999 Nov-Dec;51(6):547-9.
642. Kumari V, Mitterschiffthaler MT, Teasdale JD, Malhi GS, Brown RG, Giampietro V, et al. Neural abnormalities during cognitive generation of affect in treatment-resistant depression. *Biol Psychiatry*. 2003 Oct 15;54(8):777-91.
643. Kunik ME, Pollock BG, Perel JM, Altieri L. Clomipramine in the elderly: tolerance and plasma levels. *J Geriatr Psychiatry Neurol*. 1994 Jul-Sep;7(3):139-43.
644. Kuny S, Stassen HH. Cognitive performance in patients recovering from depression. *Psychopathology*. 1995;28(4):190-207.
645. Kupfer DJ, Spiker DG. Refractory depression: prediction of non-response by clinical indicators. *J Clin Psychiatry*. 1981 Aug;42(8):307-12.
646. Kuroda Y, Motohashi N, Ito H, Ito S, Takano A, Nishikawa T, et al. Effects of repetitive transcranial magnetic stimulation on [¹¹C]raclopride binding and cognitive function in patients with depression. *J Affect Disord*. 2006 Oct;95(1-3):35-42.
647. Kwamie Y, Persad E, Stancer H. The use of carbamazepine as an adjunctive medication in the treatment of affective disorders: a clinical report. *Can J Psychiatry*. 1984 Nov;29(7):605-8.
648. La Rue A, Spar J, Hill CD. Cognitive impairment in late-life depression: clinical correlates and treatment implications. *J Affect Disord*. 1986 Nov-Dec;11(3):179-84.
649. Laage TA. Recognizing the drug-resistant patient in anxiety and depression. *Med Clin North Am*. 1988 Jul;72(4):897-909.
650. Lader M. Quality of treatment: what do new antidepressants offer? *Int Clin Psychopharmacol*. 1995 Mar;10 Suppl 1:5-9.
651. Lam RW, Hossie H, Solomons K, Yatham LN. Citalopram and bupropion-SR: combining versus switching in patients with treatment-resistant depression. *J Clin Psychiatry*. 2004 Mar;65(3):337-40.
652. Lam RW, Wan DD, Cohen NL, Kennedy SH. Combining antidepressants for treatment-resistant depression: a review. *J Clin Psychiatry*. 2002 Aug;63(8):685-93.
653. Lambert G, Johansson M, Agren H, Friberg P. Reduced brain norepinephrine and dopamine release in treatment-refractory depressive illness: evidence in support of the catecholamine hypothesis of mood disorders. *Arch Gen Psychiatry*. 2000 Aug;57(8):787-93.
654. Lamy S, Bergsholm P, d'Elia G. The antidepressant efficacy of high-dose nondominant long-distance parietotemporal and bitemporal electroconvulsive therapy. *Convuls Ther*. 1994 Mar;10(1):43-52.

655. Landen M, Bjorling G, Agren H, Fahlen T. A randomized, double-blind, placebo-controlled trial of buspirone in combination with an SSRI in patients with treatment-refractory depression. *J Clin Psychiatry*. 1998 Dec;59(12):664-8.
656. Landen M, Hogberg P, Thase ME. Incidence of sexual side effects in refractory depression during treatment with citalopram or paroxetine. *J Clin Psychiatry*. 2005 Jan;66(1):100-6.
657. Landgrebe M, Binder H, Koller M, Eberl Y, Kleinjung T, Eichhammer P, et al. Design of a placebo-controlled, randomized study of the efficacy of repetitive transcranial magnetic stimulation for the treatment of chronic tinnitus. *BMC Psychiatry*. 2008;8:23.
658. Landgrebe M, Hauser S, Langguth B, Frick U, Hajak G, Eichhammer P. Altered cortical excitability in subjectively electrosensitive patients: results of a pilot study. *J Psychosom Res*. 2007 Mar;62(3):283-8.
659. Lang UE, Bajbouj M, Gallinat J, Hellweg R. Brain-derived neurotrophic factor serum concentrations in depressive patients during vagus nerve stimulation and repetitive transcranial magnetic stimulation. *Psychopharmacology (Berl)*. 2006 Jul;187(1):56-9.
660. Lang UE, Hellweg R, Gallinat J, Bajbouj M. Acute prefrontal cortex transcranial magnetic stimulation in healthy volunteers: no effects on brain-derived neurotrophic factor (BDNF) concentrations in serum. *J Affect Disord*. 2008 Apr;107(1-3):255-8.
661. Langer G, Karazman R, Neumark J, Saletu B, Schonbeck G, Grunberger J, et al. Isoflurane наркоtherapy in depressive patients refractory to conventional antidepressant drug treatment. A double-blind comparison with electroconvulsive treatment. *Neuropsychobiology*. 1995;31(4):182-94.
662. Langguth B, Wiegand R, Kharraz A, Landgrebe M, Marienhagen J, Frick U, et al. Pre-treatment anterior cingulate activity as a predictor of antidepressant response to repetitive transcranial magnetic stimulation (rTMS). *Neuro Endocrinol Lett*. 2007 Oct;28(5):633-8.
663. Lapid MI, Rummans TA, Pankratz VS, Appelbaum PS. Decisional capacity of depressed elderly to consent to electroconvulsive therapy. *J Geriatr Psychiatry Neurol*. 2004 Mar;17(1):42-6.
664. Lapid MI, Rummans TA, Poole KL, Pankratz VS, Maurer MS, Rasmussen KG, et al. Decisional capacity of severely depressed patients requiring electroconvulsive therapy. *J Ect*. 2003 Jun;19(2):67-72.
665. Lattanzi L, Dell'Osso L, Cassano P, Pini S, Rucci P, Houck PR, et al. Pramipexole in treatment-resistant depression: a 16-week naturalistic study. *Bipolar Disord*. 2002 Oct;4(5):307-14.
666. Lau MA. New developments in psychosocial interventions for adults with unipolar depression. *Curr Opin Psychiatry*. 2008 Jan;21(1):30-6.
667. Lauritzen L, Odgaard K, Clemmesen L, Lunde M, Ohrstrom J, Black C, et al. Relapse prevention by means of paroxetine in ECT-treated patients with major depression: a comparison with imipramine and placebo in medium-term continuation therapy. *Acta Psychiatr Scand*. 1996 Oct;94(4):241-51.
668. Lefaucheur JP, Lucas B, Andraud F, Hogrel JY, Bellivier F, Del Cul A, et al. Inter-hemispheric asymmetry of motor corticospinal excitability in major depression studied by transcranial magnetic stimulation. *J Psychiatr Res*. 2008 Apr;42(5):389-98.
669. Lehmann HE, Fenton FR, Deutsch M, Feldman S, Engelsmann F. An 11-year follow-up study of 110 depressed patients. *Acta Psychiatr Scand*. 1988 Jul;78(1):57-65.
670. Leibenluft E, Noonan BM, Wehr TA. Diurnal variation: reliability of measurement and relationship to typical and atypical symptoms of depression. *J Affect Disord*. 1992 Nov;26(3):199-204.
671. Lekwauwa R, McQuoid D, Steffens DC. Hippocampal volume is associated with physician-reported acute cognitive deficits after electroconvulsive therapy. *J Geriatr Psychiatry Neurol*. 2006 Mar;19(1):21-5.

672. Lekwauwa RE, McQuoid DR, Steffens DC. Hippocampal volume as a predictor of short-term ECT outcomes in older patients with depression. *Am J Geriatr Psychiatry*. 2005 Oct;13(10):910-3.
673. Lenox RH, Peyser JM, Rothschild B, Shipley J, Weaver L. Failure to normalize the dexamethasone suppression test: association with length of illness. *Biol Psychiatry*. 1985 Mar;20(3):333-7.
674. Lenox RH, Shipley JE, Peyser JM, Williams JM, Weaver LA. Double-blind comparison of alprazolam versus imipramine in the inpatient treatment of major depressive illness. *Psychopharmacol Bull*. 1984 Winter;20(1):79-82.
675. Lenox-Smith AJ, Jiang Q. Venlafaxine extended release versus citalopram in patients with depression unresponsive to a selective serotonin reuptake inhibitor. *Int Clin Psychopharmacol*. 2008 May;23(3):113-9.
676. Lenze EJ, Sheffrin M, Driscoll HC, Mulsant BH, Pollock BG, Dew MA, et al. Incomplete response in late-life depression: getting to remission. *Dialogues Clin Neurosci*. 2008;10(4):419-30.
677. Leonard BE. Biochemical aspects of therapy-resistant depression. *Br J Psychiatry*. 1988 Apr;152:453-9.
678. Leonard BE. Pharmacological and biochemical aspects of therapy-resistant depression. *Int Clin Psychopharmacol*. 1991 Jul;6 Suppl 1:13-28; discussion -9.
679. Lerer B, Shapira B, Calev A, Tubi N, Drexler H, Kindler S, et al. Antidepressant and cognitive effects of twice- versus three-times-weekly ECT. *Am J Psychiatry*. 1995 Apr;152(4):564-70.
680. Lestra C, d'Amato T, Ghaemmaghami C, Perret-Liaudet A, Broyer M, Renaud B, et al. Biological parameters in major depression: effects of paroxetine, viloxazine, moclobemide, and electroconvulsive therapy. Relation to early clinical outcome. *Biol Psychiatry*. 1998 Aug 15;44(4):274-80.
681. Letemendia FJ, Delva NJ, Rodenburg M, Lawson JS, Inglis J, Waldron JJ, et al. Therapeutic advantage of bifrontal electrode placement in ECT. *Psychol Med*. 1993 May;23(2):349-60.
682. Leung M, Hollander Y, Brown GR. Pretreatment with ibuprofen to prevent electroconvulsive therapy-induced headache. *J Clin Psychiatry*. 2003 May;64(5):551-3.
683. Levin GM, Bowles TM, Ehret MJ, Langae T, Tan JY, Johnson JA, et al. Assessment of human serotonin 1A receptor polymorphisms and SSRI responsiveness. *Mol Diagn Ther*. 2007;11(3):155-60.
684. Levine J. Controlled trials of inositol in psychiatry. *Eur Neuropsychopharmacol*. 1997 May;7(2):147-55.
685. Levine J, Pomerantz T, Stier S, Belmaker RH. Lack of effect of 6 g inositol treatment of post-ECT cognitive function in humans. *J Psychiatr Res*. 1995 Nov-Dec;29(6):487-9.
686. Levine J, Swartz M, Feibel H, Schreiber G. Premedication with non-selective and M1-selective muscarinic antagonists before ECT. *Isr J Psychiatry Relat Sci*. 1993;30(3):179-82.
687. Levine S. The management of resistant depression. *Acta Psychiatr Belg*. 1986 Mar-Apr;86(2):141-51.
688. Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, Daskalakis ZJ. Evidence of cortical inhibitory deficits in major depressive disorder. *Biol Psychiatry*. 2010 Mar 1;67(5):458-64.
689. Levitt AJ, Joffe RT, Kennedy SH. Bright light augmentation in antidepressant nonresponders. *J Clin Psychiatry*. 1991 Aug;52(8):336-7.
690. Levitt AJ, Wesson VA, Joffe RT. Impact of suppression of thyroxine on folate status during acute antidepressant therapy. *Psychiatry Res*. 1998 Jun 15;79(2):123-9.
691. Levy E, Margolese HC. Migraine headache prophylaxis and treatment with low-dose mirtazapine. *Int Clin Psychopharmacol*. 2003 Sep;18(5):301-3.
692. Leykin Y, Amsterdam JD, DeRubeis RJ, Gallop R, Shelton RC, Hollon SD. Progressive resistance to a selective serotonin reuptake inhibitor but not to cognitive therapy in the treatment of major depression. *J Consult Clin Psychol*. 2007 Apr;75(2):267-76.

693. Li CT, Lin CP, Chou KH, Chen IY, Hsieh JC, Wu CL, et al. Structural and cognitive deficits in remitting and non-remitting recurrent depression: a voxel-based morphometric study. *Neuroimage*. 2010 Mar;50(1):347-56.
694. Li X, Nahas Z, Kozel FA, Anderson B, Bohning DE, George MS. Acute left prefrontal transcranial magnetic stimulation in depressed patients is associated with immediately increased activity in prefrontal cortical as well as subcortical regions. *Biol Psychiatry*. 2004 May 1;55(9):882-90.
695. Li X, Nahas Z, Lomarev M, Denslow S, Shastri A, Bohning DE, et al. Prefrontal cortex transcranial magnetic stimulation does not change local diffusion: a magnetic resonance imaging study in patients with depression. *Cogn Behav Neurol*. 2003 Jun;16(2):128-35.
696. Li YS, Meyer JS, Thornby J. Longitudinal follow-up of depressive symptoms among normal versus cognitively impaired elderly. *Int J Geriatr Psychiatry*. 2001 Jul;16(7):718-27.
697. Lieb J. Lithium and antidepressants: inhibiting eicosanoids, stimulating immunity, and defeating microorganisms. *Med Hypotheses*. 2002 Oct;59(4):429-32.
698. Liebreuz M, Borgeat A, Leisinger R, Stohler R. Intravenous ketamine therapy in a patient with a treatment-resistant major depression. *Swiss Med Wkly*. 2007 Apr 21;137(15-16):234-6.
699. Lisanby SH, Devanand DP, Prudic J, Pierson D, Nobler MS, Fitzsimons L, et al. Prolactin response to electroconvulsive therapy: effects of electrode placement and stimulus dosage. *Biol Psychiatry*. 1998 Jan 15;43(2):146-55.
700. Lisanby SH, Husain MM, Rosenquist PB, Maixner D, Gutierrez R, Krystal A, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology*. 2009 Jan;34(2):522-34.
701. Lisanby SH, Maddox JH, Prudic J, Devanand DP, Sackeim HA. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry*. 2000 Jun;57(6):581-90.
702. Little A. Treatment-resistant depression. *Am Fam Physician*. 2009 Jul 15;80(2):167-72.
703. Little JD. Effect of recommended dosage range on the prescribing of antidepressants. *Aust N Z J Psychiatry*. 1995 Jun;29(2):304-8.
704. Little JT, Kimbrell TA, Wassermann EM, Grafman J, Figueras S, Dunn RT, et al. Cognitive effects of 1- and 20-hertz repetitive transcranial magnetic stimulation in depression: preliminary report. *Neuropsychiatry Neuropsychol Behav Neurol*. 2000 Apr;13(2):119-24.
705. Liu Z, Zhu F, Wang G, Xiao Z, Tang J, Liu W, et al. Association study of corticotropin-releasing hormone receptor1 gene polymorphisms and antidepressant response in major depressive disorders. *Neurosci Lett*. 2007 Mar 6;414(2):155-8.
706. Locala JA, Irefin SA, Malone D, Cywinski JB, Samuel SW, Naugle R. The comparative hemodynamic effects of methohexital and remifentanyl in electroconvulsive therapy. *J Ect*. 2005 Mar;21(1):12-5.
707. Loimer N, Hofmann P, Chaudhry HR. Midazolam shortens seizure duration following electroconvulsive therapy. *J Psychiatr Res*. 1992 Apr;26(2):97-101.
708. Lojko D, Rybakowski JK. L-thyroxine augmentation of serotonergic antidepressants in female patients with refractory depression. *J Affect Disord*. 2007 Nov;103(1-3):253-6.
709. Lomarev M, Denslow S, Nahas Z, Chae JH, George MS, Bohning DE. Vagus nerve stimulation (VNS) synchronized BOLD fMRI suggests that VNS in depressed adults has frequency/dose dependent effects. *J Psychiatr Res*. 2002 Jul-Aug;36(4):219-27.
710. Lønborg PD, Smith WT, Glaudin V, Painter JR. Short-term cotherapy with clonazepam and fluoxetine: anxiety, sleep disturbance and core symptoms of depression. *J Affect Disord*. 2000 Dec;61(1-2):73-9.

711. Loo C, Sachdev P, Elsayed H, McDarmont B, Mitchell P, Wilkinson M, et al. Effects of a 2- to 4-week course of repetitive transcranial magnetic stimulation (rTMS) on neuropsychologic functioning, electroencephalogram, and auditory threshold in depressed patients. *Biol Psychiatry*. 2001 Apr 1;49(7):615-23.
712. Loo CK, McFarquhar TF, Mitchell PB. A review of the safety of repetitive transcranial magnetic stimulation as a clinical treatment for depression. *Int J Neuropsychopharmacol*. 2008 Feb;11(1):131-47.
713. Loo CK, Mitchell PB, Croker VM, Malhi GS, Wen W, Gandevia SC, et al. Double-blind controlled investigation of bilateral prefrontal transcranial magnetic stimulation for the treatment of resistant major depression. *Psychol Med*. 2003 Jan;33(1):33-40.
714. Loo CK, Mitchell PB, McFarquhar TF, Malhi GS, Sachdev PS. A sham-controlled trial of the efficacy and safety of twice-daily rTMS in major depression. *Psychol Med*. 2007 Mar;37(3):341-9.
715. Loo CK, Sachdev P, Mitchell PB, Gandevia SC, Malhi GS, Todd G, et al. A study using transcranial magnetic stimulation to investigate motor mechanisms in psychomotor retardation in depression. *Int J Neuropsychopharmacol*. 2008 Nov;11(7):935-46.
716. Loo CK, Sachdev PS, Haindl W, Wen W, Mitchell PB, Croker VM, et al. High (15 Hz) and low (1 Hz) frequency transcranial magnetic stimulation have different acute effects on regional cerebral blood flow in depressed patients. *Psychol Med*. 2003 Aug;33(6):997-1006.
717. Lopez-Munoz F, Alamo C, Rubio G, Garcia-Garcia P, Pardo A. Reboxetine combination in treatment-resistant depression to selective serotonin reuptake inhibitors. *Pharmacopsychiatry*. 2007 Jan;40(1):14-9.
718. Lopez-Munoz F, Rubio G, Alamo C, Garcia-Garcia P, Pardo A. Reboxetine addition in patients with mirtazapine-resistant depression: a case series. *Clin Neuropharmacol*. 2006 Jul-Aug;29(4):192-6.
719. Luber B, Nobler MS, Moeller JR, Katzman GP, Prudic J, Devanand DP, et al. Quantitative EEG during seizures induced by electroconvulsive therapy: relations to treatment modality and clinical features. II. Topographic analyses. *J Ect*. 2000 Sep;16(3):229-43.
720. Luborzewski A, Schubert F, Seifert F, Danker-Hopfe H, Brakemeier EL, Schlattmann P, et al. Metabolic alterations in the dorsolateral prefrontal cortex after treatment with high-frequency repetitive transcranial magnetic stimulation in patients with unipolar major depression. *J Psychiatr Res*. 2007 Oct;41(7):606-15.
721. Lydiard RB. Tricyclic-resistant depression: treatment resistance or inadequate treatment? *J Clin Psychiatry*. 1985 Oct;46(10):412-7.
722. Lykouras E, Malliaras D, Christodoulou GN, Papakostas Y, Voulgari A, Tzonou A, et al. Delusional depression: phenomenology and response to treatment. A prospective study. *Acta Psychiatr Scand*. 1986 Mar;73(3):324-9.
723. Lykouras L, Avgoustides D, Papakostas Y, Stefanis C. Medication response to ECT-resistant melancholic patients. *Acta Psychiatr Belg*. 1995 May-Jun;95(3):113-21.
724. Lykouras L, Christodoulou GN, Malliaras D, Stefanis C. The prognostic importance of delusions in depression: a 6-year prospective follow-up study. *J Affect Disord*. 1994 Dec;32(4):233-8.
725. Lykouras L, Markianos M, Augoustides A, Papakostas Y, Stefanis C. Evaluation of TSH and prolactin responses to TRH as predictors of the therapeutic effect of ECT in depression. *Eur Neuropsychopharmacol*. 1993 Jun;3(2):81-3.
726. Lyon DE, Schubert C, Taylor AG. Pilot study of cranial stimulation for symptom management in breast cancer. *Oncol Nurs Forum*. 2010 Jul;37(4):476-83.
727. MacEwan GW, Remick RA. Treatment resistant depression: a clinical perspective. *Can J Psychiatry*. 1988 Dec;33(9):788-92.

728. Machado-Vieira R, Yuan P, Brutsche N, DiazGranados N, Luckenbaugh D, Manji HK, et al. Brain-derived neurotrophic factor and initial antidepressant response to an N-methyl-D-aspartate antagonist. *J Clin Psychiatry*. 2009 Dec;70(12):1662-6.
729. Maeda F, Keenan JP, Pascual-Leone A. Interhemispheric asymmetry of motor cortical excitability in major depression as measured by transcranial magnetic stimulation. *Br J Psychiatry*. 2000 Aug;177:169-73.
730. Maes M, Bosmans E, De Jongh R, Kenis G, Vandoolaeghe E, Neels H. Increased serum IL-6 and IL-1 receptor antagonist concentrations in major depression and treatment resistant depression. *Cytokine*. 1997 Nov;9(11):853-8.
731. Maes M, De Meester I, Verkerk R, De Medts P, Wauters A, Vanhoof G, et al. Lower serum dipeptidyl peptidase IV activity in treatment resistant major depression: relationships with immune-inflammatory markers. *Psychoneuroendocrinology*. 1997 Feb;22(2):65-78.
732. Maes M, Libbrecht I, van Hunsel F, Campens D, Meltzer HY. Pindolol and mianserin augment the antidepressant activity of fluoxetine in hospitalized major depressed patients, including those with treatment resistance. *J Clin Psychopharmacol*. 1999 Apr;19(2):177-82.
733. Maes M, Mihaylova I, Kubera M, Uytterhoeven M, Vrydags N, Bosmans E. Lower plasma Coenzyme Q10 in depression: a marker for treatment resistance and chronic fatigue in depression and a risk factor to cardiovascular disorder in that illness. *Neuro Endocrinol Lett*. 2009;30(4):462-9.
734. Maes M, Vandoolaeghe E, Desnyder R. Efficacy of treatment with trazodone in combination with pindolol or fluoxetine in major depression. *J Affect Disord*. 1996:201-10.
735. Maes M, Vandoolaeghe E, Neels H, Demedts P, Wauters A, Meltzer HY, et al. Lower serum zinc in major depression is a sensitive marker of treatment resistance and of the immune/inflammatory response in that illness. *Biol Psychiatry*. 1997 Sep 1;42(5):349-58.
736. Maes M, Verkerk R, Vandoolaeghe E, Lin A, Scharpe S. Serum levels of excitatory amino acids, serine, glycine, histidine, threonine, taurine, alanine and arginine in treatment-resistant depression: modulation by treatment with antidepressants and prediction of clinical responsiveness. *Acta Psychiatr Scand*. 1998 Apr;97(4):302-8.
737. Maes M, Verkerk R, Vandoolaeghe E, Van Hunsel F, Neels H, Wauters A, et al. Serotonin-immune interactions in major depression: lower serum tryptophan as a marker of an immune-inflammatory response. *Eur Arch Psychiatry Clin Neurosci*. 1997;247(3):154-61.
738. Magni G, Fisman M, Helmes E. Clinical correlates of ECT-resistant depression in the elderly. *J Clin Psychiatry*. 1988 Oct;49(10):405-7.
739. Malaspina D, Amador XF, Coleman EA, Mayr TL, Friedman JH, Sackeim HA. Smooth pursuit eye movement abnormality in severe major depression: effects of ECT and clinical recovery. *J Neuropsychiatry Clin Neurosci*. 1994 Winter;6(1):36-42.
740. Malaspina D, Devanand DP, Krueger RB, Prudic J, Sackeim HA. The significance of clinical EEG abnormalities in depressed patients treated with ECT. *Convuls Ther*. 1994 Dec;10(4):259-66.
741. Malhi GS. Upping the ante on antidepressants. *Bipolar Disord*. 2008 Dec;10(8):975-8.
742. Malhi GS, Ng F, Berk M. Dual-dual action? Combining venlafaxine and mirtazapine in the treatment of depression. *Aust N Z J Psychiatry*. 2008 Apr;42(4):346-9.
743. Malitz S, Sackeim HA, Decina P, Kanzler M, Kerr B. The efficacy of electroconvulsive therapy. Dose-response interactions with modality. *Ann N Y Acad Sci*. 1986;462:56-64.

744. Malsch E, Gratz I, Mani S, Backup C, Levy S, Allen E. Efficacy of electroconvulsive therapy after propofol and methohexital anesthesia. *Convuls Ther.* 1994 Sep;10(3):212-9.
745. Manji HK, Quiroz JA, Sporn J, Payne JL, Denicoff K, N AG, et al. Enhancing neuronal plasticity and cellular resilience to develop novel, improved therapeutics for difficult-to-treat depression. *Biol Psychiatry.* 2003 Apr 15;53(8):707-42.
746. Manning JS. What alternatives to first-line therapy for depression are effective? *J Clin Psychiatry.* 2010;71 Suppl 1:10-5.
747. Manning JS, Haykal RF, Connor PD, Cunningham PD, Jackson WC, Long S. Sustained remission with lamotrigine augmentation or monotherapy in female resistant depressives with mixed cyclothymic-dysthymic temperament. *J Affect Disord.* 2005 Feb;84(2-3):259-66.
748. Marangell LB. Augmentation of standard depression therapy. *Clin Ther.* 2000;22 Suppl A:A25-38; discussion A9-41.
749. Marangell LB. Switching antidepressants for treatment-resistant major depression. *J Clin Psychiatry.* 2001;62 Suppl 18:12-7.
750. Marangell LB, Rush AJ, George MS, Sackeim HA, Johnson CR, Husain MM, et al. Vagus nerve stimulation (VNS) for major depressive episodes: one year outcomes. *Biol Psychiatry.* 2002 Feb 15;51(4):280-7.
751. Marano CM, Phatak P, Vemulapalli UR, Sasan A, Nalbandyan MR, Ramanujam S, et al. Increased plasma concentration of brain-derived neurotrophic factor with electroconvulsive therapy: a pilot study in patients with major depression. *J Clin Psychiatry.* 2007 Apr;68(4):512-7.
752. Marco EJ, Wolkowitz OM, Vinogradov S, Poole JH, Lichtmacher J, Reus VI. Double-blind antigluocorticoid treatment in schizophrenia and schizoaffective disorder: a pilot study. *World J Biol Psychiatry.* 2002 Jul;3(3):156-61.
753. Markianos M, Hatzimanolis J, Lykouras L. Serotonergic and dopaminergic neuroendocrine responses of male depressive patients before and after a therapeutic ECT course. *Eur Arch Psychiatry Clin Neurosci.* 2002 Aug;252(4):172-6.
754. Markianos M, Hatzimanolis J, Lykouras L. Relationship between prolactin responses to ECT and dopaminergic and serotonergic responsivity in depressed patients. *Eur Arch Psychiatry Clin Neurosci.* 2002 Aug;252(4):166-71.
755. Markopoulou K, Papadopoulos A, Juruena MF, Poon L, Pariante CM, Cleare AJ. The ratio of cortisol/DHEA in treatment resistant depression. *Psychoneuroendocrinology.* 2009 Jan;34(1):19-26.
756. Martensson B, Bartfai A, Hallen B, Hellstrom C, Junthe T, Olander M. A comparison of propofol and methohexital as anesthetic agents for ECT: effects on seizure duration, therapeutic outcome, and memory. *Biol Psychiatry.* 1994 Feb 1;35(3):179-89.
757. Martin JL, Barbanoj MJ, Schlaepfer TE, Thompson E, Perez V, Kulisevsky J. Repetitive transcranial magnetic stimulation for the treatment of depression. Systematic review and meta-analysis. *Br J Psychiatry.* 2003 Jun;182:480-91.
758. Martiny K, Lunde M, Bech P. Transcranial low voltage pulsed electromagnetic fields in patients with treatment-resistant depression. *Biol Psychiatry.* 2010 Jul 15;68(2):163-9.
759. Martis B, Alam D, Dowd SM, Hill SK, Sharma RP, Rosen C, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin Neurophysiol.* 2003 Jun;114(6):1125-32.
760. Masand PS, Gupta S. Selective serotonin-reuptake inhibitors: an update. *Harv Rev Psychiatry.* 1999 Jul-Aug;7(2):69-84.
761. Mathew SJ. Treatment-resistant depression: recent developments and future directions. *Depress Anxiety.* 2008;25(12):989-92.
762. Matsunaga M, Okamoto Y, Suzuki S, Kinoshita A, Yoshimura S, Yoshino A, et al. Psychosocial functioning in patients with Treatment-Resistant Depression after group cognitive behavioral therapy. *BMC Psychiatry.* 2010;10:22.

763. Matura M, Fujiwara Y, Ito H, Kandatsu N, Kato N, Harada J, et al. Prolongation of QT interval induced by electroconvulsive therapy is attenuated by landiolol. *J ECT*. 2010 Mar;26(1):37-40.
764. Matters RM, Beckett WG, Kirkby KC, King TE. Recovery after electroconvulsive therapy: comparison of propofol with methohexitone anaesthesia. *Br J Anaesth*. 1995 Sep;75(3):297-300.
765. Mattes JA. Pergolide to augment the effectiveness of antidepressants: clinical experience and a small double-blind study. *Ann Clin Psychiatry*. 1997 Jun;9(2):87-8.
766. Mattes JA, Pettinati HM, Nilsen SM, Robin SE, Willis KW. Vasopressin for ECT-induced memory impairment: a placebo-controlled comparison. *Psychopharmacol Bull*. 1989;25(1):80-4.
767. Mattes JA, Pettinati HM, Stephens S, Robin SE, Willis KW. A placebo-controlled evaluation of vasopressin for ECT-induced memory impairment. *Biol Psychiatry*. 1990 Feb 1;27(3):289-303.
768. Mayberg HS. Targeted electrode-based modulation of neural circuits for depression. *J Clin Invest*. 2009 Apr;119(4):717-25.
769. Mayberg HS, Lozano AM, Voon V, McNeely HE, Seminowicz D, Hamani C, et al. Deep brain stimulation for treatment-resistant depression. *Neuron*. 2005 Mar 3;45(5):651-60.
770. Mayur P, Bray A, Fernandes J, Bythe K, Gilbert D. Impact of hyperventilation on stimulus efficiency during the early phase of an electroconvulsive therapy course: a randomized double-blind study. *J ECT*. 2010 Jun;26(2):91-4.
771. Mayur PM, Gangadhar BN, Subbakrishna DK, Janakiramaiah N. Discontinuation of antidepressant drugs during electroconvulsive therapy: a controlled study. *J Affect Disord*. 2000 Apr;58(1):37-41.
772. Mazeh D, Shahal B, Aviv A, Zemishlani H, Barak Y. A randomized, single-blind, comparison of venlafaxine with paroxetine in elderly patients suffering from resistant depression. *Int Clin Psychopharmacol* 2007:371-5.
773. Mazella J, Petrucci O, Lucas G, Deval E, Beraud-Dufour S, Gandin C, et al. Spadin, a sortilin-derived peptide, targeting rodent TREK-1 channels: a new concept in the antidepressant drug design. *PLoS Biol*. 2010;8(4):e1000355.
774. McCall WV, Colenda CC, Farah BA. Ictal EEG regularity declines during a course of RUL ECT. *Convuls Ther*. 1996 Dec;12(4):213-6.
775. McCall WV, Dunn A, Rosenquist PB. Quality of life and function after electroconvulsive therapy. *Br J Psychiatry*. 2004 Nov;185:405-9.
776. McCall WV, Dunn A, Rosenquist PB, Hughes D. Markedly suprathreshold right unilateral ECT versus minimally suprathreshold bilateral ECT: antidepressant and memory effects. *J Ect*. 2002 Sep;18(3):126-9.
777. McCall WV, Dunn AG, Rosenquist P, Hughes D. Proxy validation of patient self-reports of ADL and IADL function before and after electroconvulsive therapy. *J Ect*. 2002 Jun;18(2):74-9.
778. McCall WV, Prudic J, Olfson M, Sackeim H. Health-related quality of life following ECT in a large community sample. *J Affect Disord*. 2006 Feb;90(2-3):269-74.
779. McCall WV, Reboussin BA, Cohen W, Lawton P. Electroconvulsive therapy is associated with superior symptomatic and functional change in depressed patients after psychiatric hospitalization. *J Affect Disord*. 2001 Mar;63(1-3):17-25.
780. McCall WV, Reboussin DM, Weiner RD, Sackeim HA. Titrated moderately suprathreshold vs fixed high-dose right unilateral electroconvulsive therapy: acute antidepressant and cognitive effects. *Arch Gen Psychiatry*. 2000 May;57(5):438-44.
781. McCall WV, Shelp FE, Weiner RD, Austin S, Norris J. Convulsive threshold differences in right unilateral and bilateral ECT. *Biol Psychiatry*. 1993 Nov 1;34(9):606-11.
782. McCall WV, Zvara D, Brooker R, Arias L. Effect of esmolol pretreatment on EEG seizure morphology in RUL ECT. *Convuls Ther*. 1997 Sep;13(3):175-80.

783. McCombs J. Managing antidepressant drug therapy in an evolving marketplace. *Am J Manag Care*. 2004 Jul;10(6 Suppl):S173-8.
784. McCormick LM, Yamada T, Yeh M, Brumm MC, Thatcher RW. Antipsychotic effect of electroconvulsive therapy is related to normalization of subgenual cingulate theta activity in psychotic depression. *J Psychiatr Res*. 2009 Feb;43(5):553-60.
785. McDonald WM. Is ECT cost-effective? A critique of the National Institute of Health and Clinical Excellence's report on the economic analysis of ECT. *J Ect*. 2006 Mar;22(1):25-9.
786. McDougle CJ, Goodman WK, Leckman JF, Holzer JC, Barr LC, McCance-Katz E, et al. Limited therapeutic effect of addition of buspirone in fluvoxamine-refractory obsessive-compulsive disorder. *Am J Psychiatry*. 1993 Apr;150(4):647-9.
787. McGrath PJ, Stewart JW, Fava M, Trivedi MH, Wisniewski SR, Nierenberg AA, et al. Tranylcypromine versus venlafaxine plus mirtazapine following three failed antidepressant medication trials for depression: a STAR*D report. *Am J Psychiatry* 2006;163(9):1531-41; quiz 666.
788. McGrath PJ, Stewart JW, Nunes EN, Quitkin FM. Treatment response of depressed outpatients unresponsive to both a tricyclic and a monoamine oxidase inhibitor antidepressant. *J Clin Psychiatry*. 1994 Aug;55(8):336-9.
789. McGrath PJ, Stewart JW, Nunes EV, Ocepek-Welickson K, Rabkin JG, Quitkin FM, et al. A double-blind crossover trial of imipramine and phenelzine for outpatients with treatment-refractory depression. *Am J Psychiatry*. 1993 Jan;150(1):118-23.
790. McGrath PJ, Stewart JW, Quitkin FM, Chen Y, Alpert JE, Nierenberg AA, et al. Predictors of relapse in a prospective study of fluoxetine treatment of major depression. *Am J Psychiatry*. 2006 Sep;163(9):1542-8.
791. McIntyre J, Moral MA. Spotlight on lamotrigine for depression. *Drug News Perspect*. 2006 Sep;19(7):427-30.
792. McIntyre RS, Muller A, Mancini DA, Silver ES. What to do if an initial antidepressant fails? *Can Fam Physician*. 2003 Apr;49:449-57.
793. McIntyre RS, Soczynska JK, Konarski JZ, Kennedy SH. The effect of antidepressants on glucose homeostasis and insulin sensitivity: synthesis and mechanisms. *Expert Opin Drug Saf*. 2006 Jan;5(1):157-68.
794. McLoughlin DM. Vagus rules still apply. *Psychol Med*. 2008 May;38(5):625-7.
795. McLoughlin DM, Mogg A, Eranti S, Pluck G, Purvis R, Edwards D, et al. The clinical effectiveness and cost of repetitive transcranial magnetic stimulation versus electroconvulsive therapy in severe depression: a multicentre pragmatic randomised controlled trial and economic analysis. *Health Technol Assess*. 2007 Jul;11(24):1-54.
796. McPherson S, Cairns P, Carlyle J, Shapiro DA, Richardson P, Taylor D. The effectiveness of psychological treatments for treatment-resistant depression: a systematic review. *Acta Psychiatr Scand*. 2005 May;111(5):331-40.
797. Meats P, Timol M, Jolley D. Prognosis of depression in the elderly. *Br J Psychiatry*. 1991 Nov;159:659-63.
798. Meeks S, Looney SW, Van Haitsma K, Teri L. BE-ACTIV: a staff-assisted behavioral intervention for depression in nursing homes. *Gerontologist*. 2008 Feb;48(1):105-14.
799. Melfi CA, Chawla AJ, Croghan TW, Hanna MP, Kennedy S, Sredl K. The effects of adherence to antidepressant treatment guidelines on relapse and recurrence of depression. *Arch Gen Psychiatry*. 1998 Dec;55(12):1128-32.
800. Mendlewicz J, Hubain PP, Koumakis C. Further investigation of the dexamethasone suppression test in affective illnesses: relationship to clinical diagnosis and therapeutic response. *Neuropsychobiology*. 1984;12(1):23-6.
801. Mendlewicz J, Kriwin P, Oswald P, Souery D, Alboni S, Brunello N. Shortened onset of action of antidepressants in major depression using acetylsalicylic acid augmentation: a pilot open-label study. *Int Clin Psychopharmacol*. 2006 Jul;21(4):227-31.

802. Merrill CA, Jonsson MA, Minthon L, Ejnell H, H CsS, Blennow K, et al. Vagus nerve stimulation in patients with Alzheimer's disease: Additional follow-up results of a pilot study through 1 year. *J Clin Psychiatry*. 2006 Aug;67(8):1171-8.
803. Mervaala E, Fohr J, Kononen M, Valkonen-Korhonen M, Vainio P, Partanen K, et al. Quantitative MRI of the hippocampus and amygdala in severe depression. *Psychol Med*. 2000 Jan;30(1):117-25.
804. Metcalf G. Regulatory peptides as a source of new drugs--the clinical prospects for analogues of TRH which are resistant to metabolic degradation. *Brain Res*. 1982 Nov;257(3):389-408.
805. Meterissian GB, Bradwejn J. Comparative studies on the efficacy of psychotherapy, pharmacotherapy, and their combination in depression: was adequate pharmacotherapy provided? *J Clin Psychopharmacol*. 1989 Oct;9(5):334-9.
806. Meyers BS, Klimstra SA, Gabriele M, Hamilton M, Kakuma T, Tirumalasetti F, et al. Continuation treatment of delusional depression in older adults. *Am J Geriatr Psychiatry*. 2001 Fall;9(4):415-22.
807. Meyers BS, Mei-Tal V. Empirical study on an inpatient psychogeriatric unit: biological treatment in patients with depressive illness. *Int J Psychiatry Med*. 1985;15(2):111-24.
808. Michael N, Erfurth A, Ohrmann P, Arolt V, Heindel W, Pfleiderer B. Neurotrophic effects of electroconvulsive therapy: a proton magnetic resonance study of the left amygdalar region in patients with treatment-resistant depression. *Neuropsychopharmacology*. 2003 Apr;28(4):720-5.
809. Michalak EE, Lam RW. Breaking the myths: new treatment approaches for chronic depression. *Can J Psychiatry*. 2002 Sep;47(7):635-43.
810. Michelson D, Adler LA, Amsterdam JD, Dunner DL, Nierenberg AA, Reimherr FW, et al. Addition of atomoxetine for depression incompletely responsive to sertraline: a randomized, double-blind, placebo-controlled study. *J Clin Psychiatry*. 2007 Apr;68(4):582-7.
811. Mihaljevic-Peles A, Sagud M, Bozina N, Zivkovic M. Pharmacogenetics and antidepressant treatment in integrative psychiatry perspective. *Psychiatr Danub*. 2008 Sep;20(3):399-401.
812. Milev R, Abraham G, Hasey G, Cabaj JL. Repetitive transcranial magnetic stimulation for treatment of medication-resistant depression in older adults: a case series. *J Ect*. 2009 Mar;25(1):44-9.
813. Miller KK, Perlis RH, Papakostas GI, Mischoulon D, Losifescu DV, Brick DJ, et al. Low-dose transdermal testosterone augmentation therapy improves depression severity in women. *CNS Spectr*. 2009 Dec;14(12):688-94.
814. Miller MD, Lenze EJ, Dew MA, Whyte E, Weber E, Begley AE, et al. Effect of cerebrovascular risk factors on depression treatment outcome in later life. *Am J Geriatr Psychiatry*. 2002 Sep-Oct;10(5):592-8.
815. Miniussi C, Bonato C, Bignotti S, Gazzoli A, Gennarelli M, Pasqualetti P, et al. Repetitive transcranial magnetic stimulation (rTMS) at high and low frequency: an efficacious therapy for major drug-resistant depression? *Clin Neurophysiol*. 2005 May;116(5):1062-71.
816. Mischoulon D, Nierenberg AA, Kizilbash L, Rosenbaum JF, Fava M. Strategies for managing depression refractory to selective serotonin reuptake inhibitor treatment: a survey of clinicians. *Can J Psychiatry*. 2000 Jun;45(5):476-81.
817. Mitchell AJ, Subramaniam H. Prognosis of depression in old age compared to middle age: a systematic review of comparative studies. *Am J Psychiatry*. 2005 Sep;162(9):1588-601.
818. Mitchell P. The pharmacological treatment of tricyclic-resistant depression: review and management guidelines. *Aust N Z J Psychiatry*. 1987 Dec;21(4):442-51.
819. Mitchell P, Smythe G, Torda T. Effect of the anesthetic agent propofol on hormonal responses to ECT. *Biol Psychiatry*. 1990 Aug 15;28(4):315-24.

820. Mitchell PB, Schweitzer I, Burrows G, Johnson G, Polonowita A. Efficacy of venlafaxine and predictors of response in a prospective open-label study of patients with treatment-resistant major depression. *J Clin Psychopharmacol*. 2000 Aug;20(4):483-7.
821. Mogg A, Purvis R, Eranti S, Contell F, Taylor JP, Nicholson T, et al. Repetitive transcranial magnetic stimulation for negative symptoms of schizophrenia: a randomized controlled pilot study. *Schizophr Res*. 2007 Jul;93(1-3):221-8.
822. Moller AL, Hjaltason O, Ivarsson O, Stefansson SB. The effects of repetitive transcranial magnetic stimulation on depressive symptoms and the P(300) event-related potential. *Nord J Psychiatry*. 2006;60(4):282-5.
823. Moller HJ. Non-response to antidepressants: risk factors and therapeutic possibilities. *Int Clin Psychopharmacol*. 1994 Jun;9 Suppl 2:17-23.
824. Moller HJ, Kissling W, Baumann P, Breyer-Pfaff U, Delini-Stula A, Holsboer F, et al. Non-response to antidepressants: risk factors and therapeutic possibilities. *Pharmacopsychiatry*. 1988 Nov;21(6):285-7.
825. Moller HJ, Kissling W, Bottermann P. Serial application of clonidine tests during antidepressive treatment with chlorimipramine. *Pharmacopsychiatry*. 1984 Nov;17(6):184-7.
826. Moller HJ, Volz HP. Drug treatment of depression in the 1990s. An overview of achievements and future possibilities. *Drugs*. 1996 Nov;52(5):625-38.
827. Montgomery SA. New antidepressants and 5-HT uptake inhibitors. *Acta Psychiatr Scand Suppl*. 1989;350:107-16.
828. Moreno DH, Moreno RA, Calil HM. A Brazilian experience of treatment-resistant depression. *Int Clin Psychopharmacol*. 1994 Jun;9 Suppl 2:11-6.
829. Morishita S. Clonazepam as a therapeutic adjunct to improve the management of depression: a brief review. *Hum Psychopharmacol*. 2009 Apr;24(3):191-8.
830. Morris DW, Trivedi MH, Rush AJ. Folate and unipolar depression. *J Altern Complement Med*. 2008 Apr;14(3):277-85.
831. Morrissey JP, Steadman HJ, Burton NM. A profile of ACT recipients in New York State during 1972 and 1977. *Am J Psychiatry*. 1981 May;138(5):618-22.
832. Mosimann UP, Schmitt W, Greenberg BD, Kosel M, Muri RM, Berkhoff M, et al. Repetitive transcranial magnetic stimulation: a putative add-on treatment for major depression in elderly patients. *Psychiatry Res*. 2004 Apr 30;126(2):123-33.
833. Mu Q, Bohning DE, Nahas Z, Walker J, Anderson B, Johnson KA, et al. Acute vagus nerve stimulation using different pulse widths produces varying brain effects. *Biol Psychiatry*. 2004 Apr 15;55(8):816-25.
834. Mueller TI, Leon AC, Keller MB, Solomon DA, Endicott J, Coryell W, et al. Recurrence after recovery from major depressive disorder during 15 years of observational follow-up. *Am J Psychiatry*. 1999 Jul;156(7):1000-6.
835. Muller H, Seifert F, Weigel D, Garlichs C, Asemann R, Fluh G, et al. Vagus-nerve stimulation is tolerated in a patient with cardiac AV-Blocks. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010 Aug 16;34(6):1150.
836. Mulsant BH, Haskett RF, Prudic J, Thase ME, Malone KM, Mann JJ, et al. Low use of neuroleptic drugs in the treatment of psychotic major depression. *Am J Psychiatry*. 1997 Apr;154(4):559-61.
837. Mulsant BH, Pollock BG. Treatment-resistant depression in late life. *J Geriatr Psychiatry Neurol*. 1998 Winter;11(4):186-93.
838. Mulsant BH, Rosen J, Thornton JE, Zubenko GS. A prospective naturalistic study of electroconvulsive therapy in late-life depression. *J Geriatr Psychiatry Neurol*. 1991 Jan-Mar;4(1):3-13.
839. Murck H, Song C, Horrobin DF, Uhr M. Ethyl-eicosapentaenoate and dexamethasone resistance in therapy-refractory depression. *Int J Neuropsychopharmacol*. 2004 Sep;7(3):341-9.
840. Murphy BE. Antiglucocorticoid therapies in major depression: a review. *Psychoneuroendocrinology*. 1997;22 Suppl 1:S125-32.

841. Murphy BE, Dhar V, Ghadirian AM, Chouinard G, Keller R. Response to steroid suppression in major depression resistant to antidepressant therapy. *J Clin Psychopharmacol*. 1991 Apr;11(2):121-6.
842. Murphy BE, Ghadirian AM, Dhar V. Neuroendocrine responses to inhibitors of steroid biosynthesis in patients with major depression resistant to antidepressant therapy. *Can J Psychiatry*. 1998 Apr;43(3):279-86.
843. Murthy PJ, Gangadhar BN, Janakiramaiah N, Subbakrishna DK. Normalization of P300 amplitude following treatment in dysthymia. *Biol Psychiatry*. 1997 Oct 15;42(8):740-3.
844. Myers DH. A questionnaire study of patients' experience of electroconvulsive therapy. *J Ect*. 2007 Sep;23(3):169-74.
845. Nadeau SE, McCoy KJ, Crucian GP, Greer RA, Rossi F, Bowers D, et al. Cerebral blood flow changes in depressed patients after treatment with repetitive transcranial magnetic stimulation: evidence of individual variability. *Neuropsychiatry Neuropsychol Behav Neurol*. 2002 Sep;15(3):159-75.
846. Nahas Z, DeBrux C, Chandler V, Lorberbaum JP, Speer AM, Molloy MA, et al. Lack of significant changes on magnetic resonance scans before and after 2 weeks of daily left prefrontal repetitive transcranial magnetic stimulation for depression. *J Ect*. 2000 Dec;16(4):380-90.
847. Nahas Z, Kunik ME, Orenco CA, Molinari V, Workman R. Depression in male geropsychiatric inpatients with and without dementia: a naturalistic study. *J Affect Disord*. 1997 Dec;46(3):243-6.
848. Nahas Z, Li X, Kozel FA, Mirzki D, Memon M, Miller K, et al. Safety and benefits of distance-adjusted prefrontal transcranial magnetic stimulation in depressed patients 55-75 years of age: a pilot study. *Depress Anxiety*. 2004;19(4):249-56.
849. Nahas Z, Marangell LB, Husain MM, Rush AJ, Sackeim HA, Lisanby SH, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry*. 2005 Sep;66(9):1097-104.
850. Naish JH, Baldwin RC, Patankar T, Jeffries S, Burns AS, Taylor CJ, et al. Abnormalities of CSF flow patterns in the cerebral aqueduct in treatment-resistant late-life depression: a potential biomarker of microvascular angiopathy. *Magn Reson Med*. 2006 Sep;56(3):509-16.
851. Nakajima S, Suzuki T, Watanabe K, Kashima H, Uchida H. Accelerating response to antidepressant treatment in depression: a review and clinical suggestions. *Prog Neuropsychopharmacol Biol Psychiatry*. 2010 Mar 17;34(2):259-64.
852. Narushima K, McCormick LM, Yamada T, Thatcher RW, Robinson RG. Subgenual cingulate theta activity predicts treatment response of repetitive transcranial magnetic stimulation in participants with vascular depression. *J Neuropsychiatry Clin Neurosci*. 2010/02/18 ed 2010:75-84.
853. Navarro R, Zarkowski P, Sporn A, Avery D. Hemispheric asymmetry in resting motor threshold in major depression. *J Ect*. 2009 Mar;25(1):39-43.
854. Navarro V, Gasto C, Lomena F, Mateos JJ, Portella MJ, Masana G, et al. No brain perfusion impairment at long-term follow-up in elderly patients treated with electroconvulsive therapy for major depression. *J Ect*. 2004 Jun;20(2):89-93.
855. Navarro V, Gasto C, Lomena F, Mateos JJ, Portella MJ, Masana G, et al. Frontal cerebral perfusion after antidepressant drug treatment versus ECT in elderly patients with major depression: a 12-month follow-up control study. *J Clin Psychiatry*. 2004 May;65(5):656-61.
856. Navarro V, Gasto C, Torres X, Masana G, Penades R, Guarch J, et al. Continuation/maintenance treatment with nortriptyline versus combined nortriptyline and ECT in late-life psychotic depression: a two-year randomized study. *Am J Geriatr Psychiatry*. 2008 Jun;16(6):498-505.
857. Nelsen MR, Dunner DL. Treatment resistance in unipolar depression and other disorders. Diagnostic concerns and treatment possibilities. *Psychiatr Clin North Am*. 1993 Sep;16(3):541-66.

858. Nelsen MR, Dunner DL. Clinical and differential diagnostic aspects of treatment-resistant depression. *J Psychiatr Res.* 1995 Jan-Feb;29(1):43-50.
859. Nelson JC. Combined treatment strategies in psychiatry. *J Clin Psychiatry.* 1993 Sep;54 Suppl:42-9; discussion 55-6.
860. Nelson JC. Treatment of refractory depression. *Depress Anxiety.* 1997;5(4):165-74.
861. Nelson JC. Overcoming treatment resistance in depression. *J Clin Psychiatry.* 1998;59 Suppl 16:13-9; discussion 40-2.
862. Nelson JC. Augmentation strategies with serotonergic-noradrenergic combinations. *J Clin Psychiatry.* 1998;59 Suppl 5:65-8; discussion 9.
863. Nelson JC. Augmentation strategies in depression 2000. *J Clin Psychiatry.* 2000;61 Suppl 2:13-9.
864. Nelson JC. Managing treatment-resistant major depression. *J Clin Psychiatry.* 2003;64 Suppl 1:5-12.
865. Nelson JC. Augmentation and combination strategies in resistant depression. *J Clin Psychiatry.* 2009 Jun;70(6):e20.
866. Nelson JC, Mazure CM, Jatlow PI. Characteristics of desipramine-refractory depression. *J Clin Psychiatry.* 1994 Jan;55(1):12-9.
867. Nelson JC, Mazure CM, Jatlow PI, Bowers MB, Jr., Price LH. Combining norepinephrine and serotonin reuptake inhibition mechanisms for treatment of depression: a double-blind, randomized study. *Biol Psychiatry.* 2004 Feb 1;55(3):296-300.
868. Nemeroff CB. The clinical pharmacology and use of paroxetine, a new selective serotonin reuptake inhibitor. *Pharmacotherapy.* 1994 Mar-Apr;14(2):127-38.
869. Nemeroff CB. Augmentation strategies in patients with refractory depression. *Depress Anxiety.* 1996;4(4):169-81.
870. Nemeroff CB. Use of atypical antipsychotics in refractory depression and anxiety. *J Clin Psychiatry.* 2005;66 Suppl 8:13-21.
871. Nemeroff CB. Prevalence and management of treatment-resistant depression. *J Clin Psychiatry.* 2007;68 Suppl 8:17-25.
872. Nemeroff CB, Evans DL. Correlation between the dexamethasone suppression test in depressed patients and clinical response. *Am J Psychiatry.* 1984 Feb;141(2):247-9.
873. Nemeroff CB, Owens MJ. Treatment of mood disorders. *Nat Neurosci.* 2002 Nov;5 Suppl:1068-70.
874. Nemiah JC. Introduction. Part II. When patients don't respond: clinical strategies for managing refractory anxiety and depression. *J Clin Psychiatry.* 1994 Feb;55 Suppl:18-9.
875. Neu P, Heuser I, Bajbouj M. Cerebral blood flow during vagus nerve stimulation--a transcranial Doppler study. *Neuropsychobiology.* 2005;51(4):265-8.
876. Neuhaus AH, Gallinat J, Bajbouj M, Reischies FM. Interictal slow-wave focus in left medial temporal lobe during bilateral electroconvulsive therapy. *Neuropsychobiology.* 2005;52(4):183-9.
877. Neuhaus AH, Luborzewski A, Rentzsch J, Brakemeier EL, Opgen-Rhein C, Gallinat J, et al. P300 is enhanced in responders to vagus nerve stimulation for treatment of major depressive disorder. *J Affect Disord.* 2007 Jun;100(1-3):123-8.
878. Nierenberg AA. Treatment choice after one antidepressant fails: a survey of northeastern psychiatrists. *J Clin Psychiatry.* 1991 Sep;52(9):383-5.
879. Nierenberg AA, DeCecco LM. Definitions of antidepressant treatment response, remission, nonresponse, partial response, and other relevant outcomes: a focus on treatment-resistant depression. *J Clin Psychiatry.* 2001;62 Suppl 16:5-9.
880. Nierenberg AA, Dougherty D, Rosenbaum JF. Dopaminergic agents and stimulants as antidepressant augmentation strategies. *J Clin Psychiatry.* 1998;59 Suppl 5:60-3; discussion 4.
881. Nierenberg AA, Katz J, Fava M. A critical overview of the pharmacologic management of treatment-resistant depression. *Psychiatr Clin North Am.* 2007 Mar;30(1):13-29.

882. Nierenberg AA, McColl RD. Management options for refractory depression. *Am J Med.* 1996 Dec 30;101(6A):45S-52S.
883. Nierenberg AA, Ostacher MJ, Calabrese JR, Ketter TA, Marangell LB, Miklowitz DJ, et al. Treatment-resistant bipolar depression: a STEP-BD equipoise randomized effectiveness trial of antidepressant augmentation with lamotrigine, inositol, or risperidone. *Am J Psychiatry.* 2006 Feb;163(2):210-6.
884. Nierenberg AA, Ostacher MJ, Huffman JC, Ametrano RM, Fava M, Perlis RH. A brief review of antidepressant efficacy, effectiveness, indications, and usage for major depressive disorder. *J Occup Environ Med.* 2008 Apr;50(4):428-36.
885. Nierenberg AA, Price LH, Charney DS, Heninger GR. After lithium augmentation: a retrospective follow-up of patients with antidepressant-refractory depression. *J Affect Disord.* 1990 Mar;18(3):167-75.
886. Nikisch G, Mathe AA. CSF monoamine metabolites and neuropeptides in depressed patients before and after electroconvulsive therapy. *Eur Psychiatry.* 2008 Aug;23(5):356-9.
887. Nishihara F, Saito S. Adjustment of anaesthesia depth using bispectral index prolongs seizure duration in electroconvulsive therapy. *Anaesth Intensive Care.* 2004 Oct;32(5):661-5.
888. Nobler MS, Luber B, Moeller JR, Katzman GP, Prudic J, Devanand DP, et al. Quantitative EEG during seizures induced by electroconvulsive therapy: relations to treatment modality and clinical features. I. Global analyses. *J Ect.* 2000 Sep;16(3):211-28.
889. Nobler MS, Oquendo MA, Kegeles LS, Malone KM, Campbell CC, Sackeim HA, et al. Decreased regional brain metabolism after ect. *Am J Psychiatry.* 2001 Feb;158(2):305-8.
890. Nobler MS, Sackeim HA, Moeller JR, Prudic J, Petkova E, Waternaux C. Quantifying the speed of symptomatic improvement with electroconvulsive therapy: comparison of alternative statistical methods. *Convuls Ther.* 1997 Dec;13(4):208-21.
891. Nolen WA. Tranylcypromine in depression resistant to cyclic antidepressants. *Prog Neuropsychopharmacol Biol Psychiatry.* 1989;13(1-2):155-8.
892. Nolen WA, Bloemkolk D. Treatment of bipolar depression, a review of the literature and a suggestion for an algorithm. *Neuropsychobiology.* 2000;42 Suppl 1:11-7.
893. Nolen WA, Haffmans PM, Bouvy PF, Duivenvoorden HJ. Monoamine oxidase inhibitors in resistant major depression. A double-blind comparison of brofaromine and tranylcypromine in patients resistant to tricyclic antidepressants. *J Affect Disord.* 1993 Jul;28(3):189-97.
894. Nolen WA, Hoencamp E, Bouvy PF, Haffmans PM. Reversible monoamine oxidase-A inhibitors in resistant major depression. *Clin Neuropharmacol.* 1993;16 Suppl 2:S69-76.
895. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS. L-5HTP in depression resistant to re-uptake inhibitors. An open comparative study with tranylcypromine. *Br J Psychiatry.* 1985 Jul;147:16-22.
896. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, et al. Treatment strategy in depression. II. MAO inhibitors in depression resistant to cyclic antidepressants: two controlled crossover studies with tranylcypromine versus L-5-hydroxytryptophan and nomifensine. *Acta Psychiatr Scand.* 1988 Dec;78(6):676-83.
897. Nolen WA, van de Putte JJ, Dijken WA, Kamp JS, Blansjaar BA, Kramer HJ, et al. Treatment strategy in depression. I. Non-tricyclic and selective reuptake inhibitors in resistant depression: a double-blind partial crossover study on the effects of oxaprotiline and fluvoxamine. *Acta Psychiatr Scand.* 1988 Dec;78(6):668-75.
898. Nurnberg HG, Seidman SN, Gelenberg AJ, Fava M, Rosen R, Shabsigh R. Depression, antidepressant therapies, and erectile dysfunction: clinical trials of sildenafil citrate (Viagra) in treated and untreated patients with depression. *Urology.* 2002 Sep;60(2 Suppl 2):58-66.

899. Nutt DJ, Baldwin DS, Clayton AH, Elgie R, Lecrubier Y, Montejo AL, et al. Consensus statement and research needs: the role of dopamine and norepinephrine in depression and antidepressant treatment. *J Clin Psychiatry*. 2006;67 Suppl 6:46-9.
900. Obergriesser T, Ende G, Braus DF, Henn FA. Long-term follow-up of magnetic resonance-detectable choline signal changes in the hippocampus of patients treated with electroconvulsive therapy. *J Clin Psychiatry*. 2003 Jul;64(7):775-80.
901. O'Brien SM, Scully P, Fitzgerald P, Scott LV, Dinan TG. Plasma cytokine profiles in depressed patients who fail to respond to selective serotonin reuptake inhibitor therapy. *J Psychiatr Res*. 2007 Apr-Jun;41(3-4):326-31.
902. O'Connor DW, Gardner B, Eppingstall B, Tofler D. Cognition in elderly patients receiving unilateral and bilateral electroconvulsive therapy: a prospective, naturalistic comparison. *J Affect Disord*. 2010 Aug;124(3):235-40.
903. O'Connor KP, Colter N, Shaw JC. Cognitive style, cortical function, and electroconvulsive therapy. *J Nerv Ment Dis*. 1984 Dec;172(12):711-7.
904. O'Connor M, Brennkemeyer C, Morgan A, Bloomingdale K, Thall M, Vasile R, et al. Relative effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy on mood and memory: a neurocognitive risk-benefit analysis. *Cogn Behav Neurol*. 2003 Jun;16(2):118-27.
905. Ogawa A, Ukai S, Shinosaki K, Yamamoto M, Kawaguchi S, Ishii R, et al. Slow repetitive transcranial magnetic stimulation increases somatosensory high-frequency oscillations in humans. *Neurosci Lett*. 2004 Apr 1;358(3):193-6.
906. Ogawa K, Uema T, Motohashi N, Nishikawa M, Takano H, Hiroki M, et al. Neural mechanism of propofol anesthesia in severe depression: a positron emission tomographic study. *Anesthesiology*. 2003 May;98(5):1101-11.
907. O'Keane V, Dinan TG, Scott L, Corcoran C. Changes in hypothalamic-pituitary-adrenal axis measures after vagus nerve stimulation therapy in chronic depression. *Biol Psychiatry*. 2005 Dec 15;58(12):963-8.
908. O'Keane V, McLoughlin D, Dinan TG. D-fenfluramine-induced prolactin and cortisol release in major depression: response to treatment. *J Affect Disord*. 1992 Nov;26(3):143-50.
909. O'Leary DA, Lee AS. Seven year prognosis in depression. Mortality and readmission risk in the Nottingham ECT cohort. *Br J Psychiatry*. 1996 Oct;169(4):423-9.
910. Olver JS, Cryan JF, Burrows GD, Norman TR. Pindolol augmentation of antidepressants: a review and rationale. *Aust N Z J Psychiatry*. 2000 Feb;34(1):71-9.
911. Onder E, Tural U. Faster response in depressive patients treated with fluoxetine alone than in combination with buspirone. *J Affect Disord*. 2003 Sep;76(1-3):223-7.
912. Onishi Y, Kikuchi S, Watanabe E, Kato S. Alterations in prefrontal cortical activity in the course of treatment for late-life depression as assessed on near-infrared spectroscopy. *Psychiatry Clin Neurosci*. 2008 Apr;62(2):177-84.
913. Ontiveros A, Fontaine R, Elie R. Refractory depression: the addition of lithium to fluoxetine or desipramine. *Acta Psychiatr Scand*. 1991 Mar;83(3):188-92.
914. Oquendo MA, Malone KM, Mann JJ. Suicide: risk factors and prevention in refractory major depression. *Depress Anxiety*. 1997;5(4):202-11.
915. O'Reardon JP. Pharmacologic and therapeutic strategies in treatment-resistant depression. Introduction and clinical presentations. *CNS Spectr*. 2009 Mar;14(3 Suppl 4):4-6.
916. O'Reardon JP, Chopra MP, Bergan A, Gallop R, DeRubeis RJ, Crits-Christoph P. Response to tryptophan depletion in major depression treated with either cognitive therapy or selective serotonin reuptake inhibitor antidepressants. *Biol Psychiatry*. 2004 May 1;55(9):957-9.
917. O'Reardon JP, Cristancho P, Paliana P, Bapatla KB, Chuai S, Peshek AD. Patients with a major depressive episode responding to treatment with repetitive transcranial magnetic stimulation (rTMS) are resistant to the effects of rapid tryptophan depletion. *Depress Anxiety*. 2007;24(8):537-44.

918. O'Reardon JP, Solvason HB, Janicak PG, Sampson S, Isenberg KE, Nahas Z, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007;1208-16.
919. Orengo CA, Fullerton L, Kunik ME. Safety and efficacy of testosterone gel 1% augmentation in depressed men with partial response to antidepressant therapy. *J Geriatr Psychiatry Neurol*. 2005 Mar;18(1):20-4.
920. Oyefeso A, Valmana A, Clancy C, Ghodse H, Williams H. Fatal antidepressant overdose among drug abusers and non-drug abusers. *Acta Psychiatr Scand*. 2000 Oct;102(4):295-9.
921. Padberg F, Schule C, Zwanzger P, Baghai T, Ella R, Mikhael P, et al. Relation between responses to repetitive transcranial magnetic stimulation and partial sleep deprivation in major depression. *J Psychiatr Res*. 2002 May-Jun;36(3):131-5.
922. Padberg F, Zwanzger P, Keck ME, Kathmann N, Mikhael P, Ella R, et al. Repetitive transcranial magnetic stimulation (rTMS) in major depression: relation between efficacy and stimulation intensity. *Neuropsychopharmacology*. 2002 Oct;27(4):638-45.
923. Padberg F, Zwanzger P, Thoma H, Kathmann N, Haag C, Greenberg BD, et al. Repetitive transcranial magnetic stimulation (rTMS) in pharmacotherapy-refractory major depression: comparative study of fast, slow and sham rTMS. *Psychiatry Res* 1999;163-71.
924. Pae CU, Mandelli L, Han C, Ham BJ, Masand PS, Patkar AA, et al. Thyroid hormones affect recovery from depression during antidepressant treatment. *Psychiatry Clin Neurosci*. 2009 Jun;63(3):305-13.
925. Pae CU, Marks DM, Masand PS, Peindl K, Hooper-Wood C, Han C, et al. Methylphenidate extended release (OROS MPH) for the treatment of antidepressant-related sexual dysfunction in patients with treatment-resistant depression: results from a 4-week, double-blind, placebo-controlled trial. *Clin Neuropharmacol*. 2009 Mar-Apr;32(2):85-8.
926. Pae CU, Patkar AA, Jun TY, Lee C, Masand PS, Paik IH. Aripiprazole augmentation for treatment of patients with inadequate antidepressant response. *Depress Anxiety*. 2007;24(7):522-6.
927. Pagnin D, de Queiroz V, Pini S, Cassano GB. Efficacy of ECT in depression: a meta-analytic review. *J Ect*. 2004 Mar;20(1):13-20.
928. Pallanti S, Bernardi S, Di Rollo A, Antonini S, Quercioli L. Unilateral low frequency versus sequential bilateral repetitive transcranial magnetic stimulation: is simpler better for treatment of resistant depression? *Neuroscience*. 2010/02/11 ed 2010:323-8.
929. Pande AC, Grunhaus LJ, Aisen AM, Haskett RF. A preliminary magnetic resonance imaging study of ECT-treated depressed patients. *Biol Psychiatry*. 1990 Jan 1;27(1):102-4.
930. Pangalos MN, Malizia AL, Francis PT, Lowe SL, Bertolucci PH, Procter AW, et al. Effect of psychotropic drugs on excitatory amino acids in patients undergoing psychosurgery for depression. *Br J Psychiatry*. 1992 May;160:638-42.
931. Papakostas GI. Augmentation of standard antidepressants with atypical antipsychotic agents for treatment-resistant major depressive disorder. *Essent Psychopharmacol*. 2005;6(4):209-20.
932. Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. *J Clin Psychiatry*. 2009;70 Suppl 6:16-25.
933. Papakostas GI. Pharmacologic and therapeutic strategies in treatment-resistant depression. Switching antidepressants vs. conventional augmentation strategies. *CNS Spectr*. 2009 Mar;14(3 Suppl 4):11-4.
934. Papakostas GI, Fava M, Thase ME. Treatment of SSRI-resistant depression: a meta-analysis comparing within- versus across-class switches. *Biol Psychiatry*. 2008 Apr 1;63(7):699-704.
935. Papakostas GI, Petersen T, Denninger J, Sonawalla SB, Mahal Y, Alpert JE, et al. Somatic symptoms in treatment-resistant depression. *Psychiatry Res*. 2003 May 1;118(1):39-45.

936. Papakostas GI, Petersen T, Iosifescu DV, Roffi PA, Alpert JE, Rosenbaum JF, et al. Axis III disorders in treatment-resistant major depressive disorder. *Psychiatry Res.* 2003 May 30;118(2):183-8.
937. Papakostas GI, Petersen T, Mischoulon D, Ryan JL, Nierenberg AA, Bottiglieri T, et al. Serum folate, vitamin B12, and homocysteine in major depressive disorder, Part 1: predictors of clinical response in fluoxetine-resistant depression. *J Clin Psychiatry.* 2004 Aug;65(8):1090-5.
938. Papakostas GI, Petersen T, Worthington JJ, Roffi PA, Alpert JE, Fava M, et al. A pilot, open study of sertraline in outpatients with treatment-resistant depression (TRD) or with a history of TRD who responded but later relapsed. *Int Clin Psychopharmacol.* 2003 Sep;18(5):293-6.
939. Papakostas GI, Petersen TJ, Green C, Iosifescu DV, Yeung AS, Nierenberg AA, et al. A description of next-step switching versus augmentation practices for outpatients with treatment-resistant major depressive disorder enrolled in an academic specialty clinic. *Ann Clin Psychiatry.* 2005 Jul-Sep;17(3):161-5.
940. Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. *J Clin Psychiatry.* 2007 Jun;68(6):826-31.
941. Papakostas GI, Worthington JJ, 3rd, Iosifescu DV, Kinrys G, Burns AM, Fisher LB, et al. The combination of duloxetine and bupropion for treatment-resistant major depressive disorder. *Depress Anxiety.* 2006;23(3):178-81.
942. Papakostas Y, Markianos M, Pehlivanidis A, Papadimitriou GN, Zervas IM, Daras M, et al. Effects of thyrotropin-releasing hormone administration on the electroconvulsive therapy induced prolactin responses and seizure time. *Biol Psychiatry.* 1996 Mar 15;39(6):444-7.
943. Papakostas YG, Markianos M, Zervas IM, Theodoropoulou M, Vaidakis N, Daras M. Administration of citalopram before ECT: seizure duration and hormone responses. *J Ect.* 2000 Dec;16(4):356-60.
944. Papavasiliou PS, Miller ST, Palat G, Pleban P, Mostek W. Selective disturbances of serum mineral profiles by electroconvulsive therapy. *J Nerv Ment Dis.* 1985 Jul;173(7):401-5.
945. Pardo JV, Sheikh SA, Kuskowski MA, Surerus-Johnson C, Hagen MC, Lee JT, et al. Weight loss during chronic, cervical vagus nerve stimulation in depressed patients with obesity: an observation. *Int J Obes (Lond).* 2007 Nov;31(11):1756-9.
946. Pardo JV, Sheikh SA, Schwindt GC, Lee JT, Kuskowski MA, Surerus C, et al. Chronic vagus nerve stimulation for treatment-resistant depression decreases resting ventromedial prefrontal glucose metabolism. *Neuroimage.* 2008 Aug 15;42(2):879-89.
947. Parker G, Hadzi-Pavlovic D, Hickie I, Mitchell P, Wilhelm K, Brodaty H, et al. Psychotic depression: a review and clinical experience. *Aust N Z J Psychiatry.* 1991 Jun;25(2):169-80.
948. Parker G, Roy K, Wilhelm K, Mitchell P. Assessing the comparative effectiveness of antidepressant therapies: a prospective clinical practice study. *J Clin Psychiatry.* 2001 Feb;62(2):117-25.
949. Pary R, Tobias CR, Lippmann S. Pharmacologic treatment strategies for the depressed, poorly responsive patient. *South Med J.* 1992 Nov;85(11):1122-6, 30.
950. Pascual-Leone A, Rubio B, Pallardo F, Catala MD. Rapid-rate transcranial magnetic stimulation of left dorsolateral prefrontal cortex in drug-resistant depression. *Lancet.* 1996 Jul 27;348(9022):233-7.
951. Passard A, Attal N, Benadhira R, Brasseur L, Saba G, Sichere P, et al. Effects of unilateral repetitive transcranial magnetic stimulation of the motor cortex on chronic widespread pain in fibromyalgia. *Brain.* 2007 Oct;130(Pt 10):2661-70.
952. Patankar TF, Baldwin R, Mitra D, Jeffries S, Sutcliffe C, Burns A, et al. Virchow-Robin space dilatation may predict resistance to antidepressant monotherapy in elderly patients with depression. *J Affect Disord.* 2007 Jan;97(1-3):265-70.

953. Patkar AA, Pae CU, Masand PS. Transdermal selegiline: the new generation of monoamine oxidase inhibitors. *CNS Spectr*. 2006 May;11(5):363-75.
954. Patkar AA, Pae CU, Zarzar M. Transdermal selegiline. *Drugs Today (Barc)*. 2007 Jun;43(6):361-77.
955. Patten SB, Lupin DA, Boucher SA, Lamarre CJ. Pharmacologic management of refractory depression. *Cmaj*. 1992 Feb 15;146(4):483-7.
956. Payne ME, Hybels CF, Bales CW, Steffens DC. Vascular nutritional correlates of late-life depression. *Am J Geriatr Psychiatry*. 2006 Sep;14(9):787-95.
957. Penttila J, Paillere-Martinot ML, Martinot JL, Ringuenet D, Wessa M, Houenou J, et al. Cortical folding in patients with bipolar disorder or unipolar depression. *J Psychiatry Neurosci*. 2009 Mar;34(2):127-35.
958. Perera TD, Luber B, Nobler MS, Prudic J, Anderson C, Sackeim HA. Seizure expression during electroconvulsive therapy: relationships with clinical outcome and cognitive side effects. *Neuropsychopharmacology*. 2004 Apr;29(4):813-25.
959. Peretti CS, Danion JM, Grange D, Mobarek N. Bilateral ECT and autobiographical memory of subjective experiences related to melancholia: a pilot study. *J Affect Disord*. 1996 Nov 4;41(1):9-15.
960. Perez V, Soler J, Puigdemont D, Alvarez E, Artigas F. A double-blind, randomized, placebo-controlled trial of pindolol augmentation in depressive patients resistant to serotonin reuptake inhibitors. *Grup de Recerca en Trastorns Afectius. Arch Gen Psychiatry*. 1999 Apr;56(4):375-9.
961. Perlis RH, Alpert J, Nierenberg AA, Mischoulon D, Yeung A, Rosenbaum JF, et al. Clinical and sociodemographic predictors of response to augmentation, or dose increase among depressed outpatients resistant to fluoxetine 20 mg/day. *Acta Psychiatr Scand*. 2003 Dec;108(6):432-8.
962. Perlis RH, Iosifescu DV, Alpert J, Nierenberg AA, Rosenbaum JF, Fava M. Effect of medical comorbidity on response to fluoxetine augmentation or dose increase in outpatients with treatment-resistant depression. *Psychosomatics*. 2004 May-Jun;45(3):224-9.
963. Perry EB, Berman RM, Sanacora G, Anand A, Lynch-Colonese K, Charney DS. Pindolol augmentation in depressed patients resistant to selective serotonin reuptake inhibitors: a double-blind, randomized, controlled trial. *J Clin Psychiatry*. 2004 Feb;65(2):238-43.
964. Perry PJ, Morgan DE, Smith RE, Tsuang MT. Treatment of unipolar depression accompanied by delusions. ECT versus tricyclic antidepressant-antipsychotic combinations. *J Affect Disord*. 1982 Sep;4(3):195-200.
965. Perry SW, 3rd. HIV-related depression. *Res Publ Assoc Res Nerv Ment Dis*. 1994;72:223-38.
966. Perugi G, Akiskal HS, Micheli C, Toni C, Madaro D. Clinical characterization of depressive mixed state in bipolar-I patients: Pisa-San Diego collaboration. *J Affect Disord*. 2001 Dec;67(1-3):105-14.
967. Peschina W, Conca A, Konig P, Fritzsche H, Beraus W. Low frequency rTMS as an add-on antidepressive strategy: heterogeneous impact on 99mTc-HMPAO and 18 F-FDG uptake as measured simultaneously with the double isotope SPECT technique. Pilot study. *Nucl Med Commun*. 2001 Aug;22(8):867-73.
968. Peters EJ, Slager SL, Kraft JB, Jenkins GD, Reinalda MS, McGrath PJ, et al. Pharmacokinetic genes do not influence response or tolerance to citalopram in the STAR*D sample. *PLoS One*. 2008;3(4):e1872.
969. Peters EJ, Slager SL, McGrath PJ, Knowles JA, Hamilton SP. Investigation of serotonin-related genes in antidepressant response. *Mol Psychiatry*. 2004 Sep;9(9):879-89.
970. Petersen T, Papakostas GI, Posternak MA, Kant A, Guyker WM, Iosifescu DV, et al. Empirical testing of two models for staging antidepressant treatment resistance. *J Clin Psychopharmacol*. 2005 Aug;25(4):336-41.

971. Petrides G, Fink M, Husain MM, Knapp RG, Rush AJ, Mueller M, et al. ECT remission rates in psychotic versus nonpsychotic depressed patients: a report from CORE. *J Ect*. 2001 Dec;17(4):244-53.
972. Pettinati HM, Nilsen S. Missed and brief seizures during ECT: differential response between unilateral and bilateral electrode placement. *Biol Psychiatry*. 1985 May;20(5):506-14.
973. Pettinati HM, Rosenberg J. Memory self-ratings before and after electroconvulsive therapy: depression-versus ECT induced. *Biol Psychiatry*. 1984 Apr;19(4):539-48.
974. Phanjoo A. The elderly depressed and treatment with fluvoxamine. *Int Clin Psychopharmacol*. 1991 Dec;6 Suppl 3:33-7; discussion 7-9.
975. Philip NS, Carpenter LL, Tyrka AR, Price LH. Augmentation of antidepressants with atypical antipsychotics: a review of the current literature. *J Psychiatr Pract*. 2008 Jan;14(1):34-44.
976. Philip NS, Carpenter LL, Tyrka AR, Price LH. Pharmacologic approaches to treatment resistant depression: a re-examination for the modern era. *Expert Opin Pharmacother*. 2010 Apr;11(5):709-22.
977. Phillips KA. Body dysmorphic disorder: diagnostic controversies and treatment challenges. *Bull Menninger Clin*. 2000 Winter;64(1):18-35.
978. Phillips KA, Nierenberg AA. The assessment and treatment of refractory depression. *J Clin Psychiatry*. 1994 Feb;55 Suppl:20-6.
979. Pinar M, Gulsun M, Tasci I, Erdil A, Bolu E, Acikel C, et al. Maprotiline induced weight gain in depressive disorder: changes in circulating ghrelin and adiponectin levels and insulin sensitivity. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008 Jan 1;32(1):135-9.
980. Pisvejc J, Hyrman V, Sikora J, Berankova A, Kobeda B, Auerova M, et al. A comparison of brief and ultrabrief pulse stimuli in unilateral ECT. *J Ect*. 1998 Jun;14(2):68-75.
981. Pluijms EM, Birkenhager TK, Huijbrechts IP, Moleman P. Influence of resistance to antidepressant pharmacotherapy on short-term response to electroconvulsive therapy. *J Affect Disord*. 2002 May;69(1-3):93-9.
982. Podawiltz A, Culpepper L. Treatment-resistant depression in Hispanic patients. *J Clin Psychiatry*. 2010 Jun;71(6):e12.
983. Pogarell O, Koch W, Popperl G, Tatsch K, Jakob F, Mulert C, et al. Acute prefrontal rTMS increases striatal dopamine to a similar degree as D-amphetamine. *Psychiatry Res*. 2007 Dec 15;156(3):251-5.
984. Poirier MF, Boyer P. Venlafaxine and paroxetine in treatment-resistant depression. Double-blind, randomised comparison. *Br J Psychiatry* 1999:12-6.
985. Pope HG, Jr., Cohane GH, Kanayama G, Siegel AJ, Hudson JI. Testosterone gel supplementation for men with refractory depression: a randomized, placebo-controlled trial. *Am J Psychiatry*. 2003 Jan;160(1):105-11.
986. Posternak MA, Solomon DA, Leon AC, Mueller TI, Shea MT, Endicott J, et al. The naturalistic course of unipolar major depression in the absence of somatic therapy. *J Nerv Ment Dis*. 2006 May;194(5):324-9.
987. Posternak MA, Zimmerman M. Short-term spontaneous improvement rates in depressed outpatients. *J Nerv Ment Dis*. 2000 Dec;188(12):799-804.
988. Poulet E, Brunelin J, Boeuvre C, Lerond J, D'Amato T, Dalery J, et al. Repetitive transcranial magnetic stimulation does not potentiate antidepressant treatment. *Eur Psychiatry*. 2004 Sep;19(6):382-3.
989. Powers RH, Kniesner TJ, Croghan TW. Psychotherapy and pharmacotherapy in depression. *J Ment Health Policy Econ*. 2002 Dec;5(4):153-61.
990. Preskorn SH. Treatment options for the patient who does not respond well to initial antidepressant therapy. *J Psychiatr Pract*. 2009 May;15(3):202-10.
991. Preskorn SH. Outliers on the dose-response curve: how to minimize this problem using therapeutic drug monitoring, an underutilized tool in psychiatry. *J Psychiatr Pract*. 2010 May;16(3):177-82.

992. Preskorn SH, Baker B, Kolluri S, Menniti FS, Krams M, Landen JW. An innovative design to establish proof of concept of the antidepressant effects of the NR2B subunit selective N-methyl-D-aspartate antagonist, CP-101,606, in patients with treatment-refractory major depressive disorder. *J Clin Psychopharmacol.* 2008 Dec;28(6):631-7.
993. Price GW, Lee JW, Garvey CA, Gibson N. The use of background EEG activity to determine stimulus timing as a means of improving rTMS efficacy in the treatment of depression: a controlled comparison with standard techniques. *Brain Stimul.* 2010 Jul;3(3):140-52.
994. Price LH, Charney DS, Delgado PL, Heninger GR. Fenfluramine augmentation in tricyclic-refractory depression. *J Clin Psychopharmacol.* 1990 Oct;10(5):312-7.
995. Price LH, Charney DS, Heninger GR. Efficacy of lithium-tranylcypromine treatment in refractory depression. *Am J Psychiatry.* 1985 May;142(5):619-23.
996. Price LH, Charney DS, Heninger GR. Variability of response to lithium augmentation in refractory depression. *Am J Psychiatry.* 1986 Nov;143(11):1387-92.
997. Price LH, Charney DS, Heninger GR. Reserpine augmentation of desipramine in refractory depression: clinical and neurobiological effects. *Psychopharmacology (Berl).* 1987;92(4):431-7.
998. Pridmore S. Substitution of rapid transcranial magnetic stimulation treatments for electroconvulsive therapy treatments in a course of electroconvulsive therapy. *Depress Anxiety.* 2000;12(3):118-23.
999. Pridmore S, Turnier-Shea Y. Medication options in the treatment of treatment-resistant depression. *Aust N Z J Psychiatry.* 2004 Apr;38(4):219-25.
1000. Priest R. Therapy-resistant depression. Workshop report. *Int Clin Psychopharmacol.* 1993 Jan;7(3-4):201-2.
1001. Prohovnik I, Sackeim HA, Decina P, Malitz S. Acute reductions of regional cerebral blood flow following electroconvulsive therapy. Interactions with modality and time. *Ann N Y Acad Sci.* 1986;462:249-62.
1002. Prudic J, Fitzsimons L, Nobler MS, Sackeim HA. Naloxone in the prevention of the adverse cognitive effects of ECT: a within-subject, placebo controlled study. *Neuropsychopharmacology.* 1999 Aug;21(2):285-93.
1003. Prudic J, Haskett RF, Mulsant B, Malone KM, Pettinati HM, Stephens S, et al. Resistance to antidepressant medications and short-term clinical response to ECT. *Am J Psychiatry.* 1996 Aug;153(8):985-92.
1004. Prudic J, Olfson M, Marcus SC, Fuller RB, Sackeim HA. Effectiveness of electroconvulsive therapy in community settings. *Biol Psychiatry.* 2004 Feb 1;55(3):301-12.
1005. Prudic J, Sackeim HA, Decina P, Hopkins N, Ross FR, Malitz S. Acute effects of ECT on cardiovascular functioning: relations to patient and treatment variables. *Acta Psychiatr Scand.* 1987 Apr;75(4):344-51.
1006. Prudic J, Sackeim HA, Devanand DP, Krueger RB, Settembrino JM. Acute cognitive effects of subconvulsive electrical stimulation. *Convuls Ther.* 1994 Mar;10(1):4-24.
1007. Quilty LC, De Fruyt F, Rolland JP, Kennedy SH, Rouillon PF, Bagby RM. Dimensional personality traits and treatment outcome in patients with major depressive disorder. *J Affect Disord.* 2008 Jun;108(3):241-50.
1008. Quitkin FM. The importance of dosage in prescribing antidepressants. *Br J Psychiatry.* 1985 Dec;147:593-7.
1009. Quitkin FM, McGrath P, Liebowitz MR, Stewart J, Howard A. Monoamine oxidase inhibitors in bipolar endogenous depressives. *J Clin Psychopharmacol.* 1981 Mar;1(2):70-4.
1010. Rabins PV, Pearlson GD, Aylward E, Kumar AJ, Dowell K. Cortical magnetic resonance imaging changes in elderly inpatients with major depression. *Am J Psychiatry.* 1991 May;148(5):617-20.
1011. Rado J, Janicak PG. Vagus nerve stimulation for severe depression. *J Psychosoc Nurs Ment Health Serv.* 2007 Jul;45(7):43-51.

1012. Railton R, Fisher J, Sinclair A, Shrigmankar JM. Comparison of electrical measurements on constant voltage and constant current ECT machines. *Br J Psychiatry*. 1987 Aug;151:244-7.
1013. Ramasubbu R. Insulin resistance: a metabolic link between depressive disorder and atherosclerotic vascular diseases. *Med Hypotheses*. 2002 Nov;59(5):537-51.
1014. Rami L, Goti J, Ferrer J, Marcos T, Salamero M, Bernardo M. Cognitive functions after only one ECT session: a controlled study. *Psychiatry Res*. 2008 Apr 15;158(3):389-94.
1015. Ranjkesh F, Barekataan M, Akuchakian S. Bifrontal versus right unilateral and bitemporal electroconvulsive therapy in major depressive disorder. *J Ect*. 2005 Dec;21(4):207-10.
1016. Rasgon NL, Kenna HA, Williams KE, Powers B, Wroolie T, Schatzberg AF. Rosiglitazone add-on in treatment of depressed patients with insulin resistance: a pilot study. *ScientificWorldJournal*. 2010;10:321-8.
1017. Rasmussen KG, Black JL. Serotonin transporter gene status and electroconvulsive therapy outcomes: a retrospective analysis of 83 patients. *J Clin Psychiatry*. 2009 Jan;70(1):92-4.
1018. Rasmussen KG, Knapp RG, Biggs MM, Smith GE, Rummans TA, Petrides G, et al. Data management and design issues in an unmasked randomized trial of electroconvulsive therapy for relapse prevention of severe depression: the consortium for research in electroconvulsive therapy trial. *J Ect*. 2007 Dec;23(4):244-50.
1019. Rasmussen KG, Mueller M, Rummans TA, Husain MM, Petrides G, Knapp RG, et al. Is baseline medication resistance associated with potential for relapse after successful remission of a depressive episode with ECT? Data from the Consortium for Research on Electroconvulsive Therapy (CORE). *J Clin Psychiatry*. 2009 Feb;70(2):232-7.
1020. Rasmussen KG, Snyder KA, Knapp RG, Mueller M, Yim E, Husain MM, et al. Relationship between somatization and remission with ECT. *Psychiatry Res*. 2004 Dec 30;129(3):293-5.
1021. Rasmussen LB, Mikkelsen K, Haugen M, Pripp AH, Forre OT. Treatment of fibromyalgia at the Maharishi Ayurveda Health Centre in Norway. A six-month follow-up study. *Clin Exp Rheumatol*. 2009 Sep-Oct;27(5 Suppl 56):S46-50.
1022. Rasmussen NA, Schroder P, Olsen LR, Brodsgaard M, Unden M, Bech P. Modafinil augmentation in depressed patients with partial response to antidepressants: a pilot study on self-reported symptoms covered by the Major Depression Inventory (MDI) and the Symptom Checklist (SCL-92). *Nord J Psychiatry*. 2005;59(3):173-8.
1023. Rasmussen-Torvik LJ, McAlpine DD. Genetic screening for SSRI drug response among those with major depression: great promise and unseen perils. *Depress Anxiety*. 2007;24(5):350-7.
1024. Ravindran AV. If a patient does not respond to a full dose of fluvoxamine for at least 12 weeks, what alternatives should be considered? *J Psychiatry Neurosci*. 1998 Mar;23(2):136.
1025. Recart A, Rawal S, White PF, Byerly S, Thornton L. The effect of remifentanyl on seizure duration and acute hemodynamic responses to electroconvulsive therapy. *Anesth Analg*. 2003 Apr;96(4):1047-50, table of contents.
1026. Regenold WT, Hisley KC, Obuchowski A, Lefkowitz DM, Marano C, Hauser P. Relationship of white matter hyperintensities to cerebrospinal fluid glucose polyol pathway metabolites-a pilot study in treatment-resistant affective disorder patients. *J Affect Disord*. 2005 Apr;85(3):341-50.
1027. Regestein QR, Monk TH. Delayed sleep phase syndrome: a review of its clinical aspects. *Am J Psychiatry*. 1995 Apr;152(4):602-8.
1028. Reimherr F, Amsterdam J, Dunner D, Adler L, Zhang S, Williams D, et al. Genetic polymorphisms in the treatment of depression: speculations from an augmentation study using atomoxetine. *Psychiatry Res*. 2010 Jan 30;175(1-2):67-73.
1029. Remick RA. Treatment resistant depression. *Psychiatr J Univ Ott*. 1989 Jun;14(2):394-6.

1030. Repo-Tiihonen E, Eloranta A, Hallikainen T, Tiihonen J. Effects of venlafaxine treatment on clozapine plasma levels in schizophrenic patients. *Neuropsychobiology*. 2005;51(4):173-6.
1031. Reus VI. Management of treatment-resistant unipolar and chronically depressed patients. *Psychiatr Clin North Am*. 1996 Jun;19(2):201-13.
1032. Rich CL, Spiker DG, Jewell SW, Neil JF, Phillipson M. ECT response in psychotic versus nonpsychotic unipolar depressives. *J Clin Psychiatry*. 1986 Mar;47(3):123-5.
1033. Richelson E. Treatment of acute depression. *Psychiatr Clin North Am*. 1993 Sep;16(3):461-78.
1034. Riddle WJ, Scott AI, Bennie J, Carroll S, Fink G. Current intensity and oxytocin release after electroconvulsive therapy. *Biol Psychiatry*. 1993 Jun 1-15;33(11-12):839-41.
1035. Robin A, De Tissera S. A double-blind controlled comparison of the therapeutic effects of low and high energy electroconvulsive therapies. *Br J Psychiatry*. 1982 Oct;141:357-66.
1036. Robinson RG, Tenev V, Jorge RE. Citalopram for continuation therapy after repetitive transcranial magnetic stimulation in vascular depression. *Am J Geriatr Psychiatry*. 2009 Aug;17(8):682-7.
1037. Rocca P, Marchiaro L, Rasetti R, Rivoira E, Bogetto F. A comparison of paroxetine versus paroxetine plus amisulpride in the treatment of dysthymic disorder: efficacy and psychosocial outcomes. *Psychiatry Res*. 2002 Oct 10;112(2):145-52.
1038. Rodger CR, Scott AI, Whalley LJ. Is there a delay in the onset of the antidepressant effect of electroconvulsive therapy? *Br J Psychiatry*. 1994 Jan;164(1):106-9.
1039. Roemer RA, Shagass C, Dubin W, Jaffe R, Katz R. Relationship between pretreatment electroencephalographic coherence measures and subsequent response to electroconvulsive therapy: a preliminary study. *Neuropsychobiology*. 1990;24(3):121-4.
1040. Rogoz Z, Dziedzicka-Wasylewska M, Daniel WA, Wojcikowski J, Dudek D, Wrobel A, et al. Effects of joint administration of imipramine and amantadine in patients with drug-resistant unipolar depression. *Pol J Pharmacol*. 2004 Nov-Dec;56(6):735-42.
1041. Rogoz Z, Skuza G, Daniel WA, Wojcikowski J, Dudek D, Wrobel A. Amantadine as an additive treatment in patients suffering from drug-resistant unipolar depression. *Pharmacol Rep*. 2007 Nov-Dec;59(6):778-84.
1042. Rogoz Z, Skuza G, Wojcikowski J, Daniel WA, Wrobel A, Dudek D, et al. Effect of metyrapone supplementation on imipramine therapy in patients with treatment-resistant unipolar depression. *Pol J Pharmacol*. 2004 Nov-Dec;56(6):849-55.
1043. Rohan KJ, Lindsey KT, Roecklein KA, Lacy TJ. Cognitive-behavioral therapy, light therapy, and their combination in treating seasonal affective disorder. *J Affect Disord*. 2004 Jun;80(2-3):273-83.
1044. Rohland BM. Self-report of improvement following hospitalization for electroconvulsive therapy: relationship to functional status and service use. *Adm Policy Ment Health*. 2001 Jan;28(3):193-203.
1045. Ros S, Aguera L, de la Gandara J, Rojo JE, de Pedro JM. Potentiation strategies for treatment-resistant depression. *Acta Psychiatr Scand Suppl*. 2005(428):14-24, 36.
1046. Rosa MA, Gattaz WF, Pascual-Leone A, Fregni F, Rosa MO, Rumi DO, et al. Comparison of repetitive transcranial magnetic stimulation and electroconvulsive therapy in unipolar non-psychotic refractory depression: a randomized, single-blind study. *Int J Neuropsychopharmacol*. 2006 Dec;9(6):667-76.
1047. Rosa MA, Rosa MO, Marcolin MA, Fregni F. Cardiovascular effects of anesthesia in ECT: a randomized, double-blind comparison of etomidate, propofol, and thiopental. *J Ect*. 2007 Mar;23(1):6-8.
1048. Rosen I, Silfverskiold P. Quantification of EEG changes following electroconvulsive therapy in depression. *Eur Arch Psychiatry Neurol Sci*. 1987;236(4):209-13.

1049. Rosenbaum JF. Treatment-resistant panic disorder. *J Clin Psychiatry*. 1997;58 Suppl 2:61-4; discussion 5.
1050. Rosenquist PB, Dunn A, Rapp S, Gaba A, McCall WV. What predicts patients' expressed likelihood of choosing electroconvulsive therapy as a future treatment option? *J Ect*. 2006 Mar;22(1):33-7.
1051. Rosenzweig-Lipson S, Beyer CE, Hughes ZA, Khawaja X, Rajarao SJ, Malberg JE, et al. Differentiating antidepressants of the future: efficacy and safety. *Pharmacol Ther*. 2007 Jan;113(1):134-53.
1052. Rossini D, Lucca A, Magri L, Malaguti A, Smeraldi E, Colombo C, et al. A symptom-specific analysis of the effect of high-frequency left or low-frequency right transcranial magnetic stimulation over the dorsolateral prefrontal cortex in major depression. *Neuropsychobiology*. 2010;62(2):91-7.
1053. Rossini D, Lucca A, Zanardi R, Magri L, Smeraldi E. Transcranial magnetic stimulation in treatment-resistant depressed patients: a double-blind, placebo-controlled trial. *Psychiatry Res*. 2005 Nov 15;137(1-2):1-10.
1054. Rossini D, Magri L, Lucca A, Giordani S, Smeraldi E, Zanardi R. Does rTMS hasten the response to escitalopram, sertraline, or venlafaxine in patients with major depressive disorder? A double-blind, randomized, sham-controlled trial. *J Clin Psychiatry*. 2005 Dec;66(12):1569-75.
1055. Rouillon F, Gorwood P. The use of lithium to augment antidepressant medication. *J Clin Psychiatry*. 1998;59 Suppl 5:32-9; discussion 40-1.
1056. Rubin EH, Kinscherf DA, Figiel GS, Zorumski CF. The nature and time course of cognitive side effects during electroconvulsive therapy in the elderly. *J Geriatr Psychiatry Neurol*. 1993 Apr-Jun;6(2):78-83.
1057. Rubin RR, Gaussoin SA, Peyrot M, DiLillo V, Miller K, Wadden TA, et al. Cardiovascular disease risk factors, depression symptoms and antidepressant medicine use in the Look AHEAD (Action for Health in Diabetes) clinical trial of weight loss in diabetes. *Diabetologia*. 2010 Aug;53(8):1581-9.
1058. Rubio G, San L, Lopez-Munoz F, Alamo C. Reboxetine adjunct for partial or nonresponders to antidepressant treatment. *J Affect Disord*. 2004 Jul;81(1):67-72.
1059. Rudas S, Schmitz M, Pichler P, Baumgartner A. Treatment of refractory chronic depression and dysthymia with high-dose thyroxine. *Biol Psychiatry*. 1999 Jan 15;45(2):229-33.
1060. Ruhe HG, Huyser J, Swinkels JA, Schene AH. Switching antidepressants after a first selective serotonin reuptake inhibitor in major depressive disorder: a systematic review. *J Clin Psychiatry*. 2006 Dec;67(12):1836-55.
1061. Rumi DO, Gattaz WF, Rigonatti SP, Rosa MA, Fregni F, Rosa MO, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry*. 2005 Jan 15;57(2):162-6.
1062. Rush AJ, Bose A, Heydorn WE. Naturalistic study of the early psychiatric use of citalopram in the United States. *Depress Anxiety*. 2002;16(3):121-7.
1063. Rush AJ, Sackeim HA, Marangell LB, George MS, Brannan SK, Davis SM, et al. Effects of 12 months of vagus nerve stimulation in treatment-resistant depression: a naturalistic study. *Biol Psychiatry*. 2005 Sep 1;58(5):355-63.
1064. Rush AJ, Siefert SE. Clinical issues in considering vagus nerve stimulation for treatment-resistant depression. *Exp Neurol*. 2009 Sep;219(1):36-43.
1065. Rush AJ, Thase ME, Dube S. Research issues in the study of difficult-to-treat depression. *Biol Psychiatry*. 2003 Apr 15;53(8):743-53.

1066. Russell JL. Relatively low doses of cisapride in the treatment of nausea in patients treated with venlafaxine for treatment-refractory depression. *J Clin Psychopharmacol.* 1996 Feb;16(1):35-7.
1067. Russell JM, Hawkins K, Ozminkowski RJ, Orsini L, Crown WH, Kennedy S, et al. The cost consequences of treatment-resistant depression. *J Clin Psychiatry.* 2004 Mar;65(3):341-7.
1068. Rutherford B, Sneed J, Miyazaki M, Eisenstadt R, Devanand D, Sackeim H, et al. An open trial of aripiprazole augmentation for SSRI non-remitters with late-life depression. *Int J Geriatr Psychiatry.* 2007 Oct;22(10):986-91.
1069. Rybakowski J, Matkowski K. Adding lithium to antidepressant therapy: factors related to therapeutic potentiation. *Eur Neuropsychopharmacol.* 1992 Jun;2(2):161-5.
1070. Rybakowski JK, Suwalska A, Chlopocka-Wozniak M. Potentiation of antidepressants with lithium or carbamazepine in treatment-resistant depression. *Neuropsychobiology.* 1999 Sep;40(3):134-9.
1071. Rybakowski JK, Suwalska A, Lojko D, Rymaszewska J, Kiejna A. Bipolar mood disorders among Polish psychiatric outpatients treated for major depression. *J Affect Disord.* 2005 Feb;84(2-3):141-7.
1072. Sachs GS. Treatment-resistant bipolar depression. *Psychiatr Clin North Am.* 1996 Jun;19(2):215-36.
1073. Sackeim H, Decina P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. Effects of sex, age, electrode placement, and number of treatments. *Arch Gen Psychiatry.* 1987 Apr;44(4):355-60.
1074. Sackeim HA. Continuation therapy following ECT: directions for future research. *Psychopharmacol Bull.* 1994;30(3):501-21.
1075. Sackeim HA. The definition and meaning of treatment-resistant depression. *J Clin Psychiatry.* 2001;62 Suppl 16:10-7.
1076. Sackeim HA, Brannan SK, Rush AJ, George MS, Marangell LB, Allen J. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol.* 2007 Dec;10(6):817-26.
1077. Sackeim HA, Decina P, Kanzler M, Kerr B, Malitz S. Effects of electrode placement on the efficacy of titrated, low-dose ECT. *Am J Psychiatry.* 1987 Nov;144(11):1449-55.
1078. Sackeim HA, Decina P, Portnoy S, Neeley P, Malitz S. Studies of dosage, seizure threshold, and seizure duration in ECT. *Biol Psychiatry.* 1987 Mar;22(3):249-68.
1079. Sackeim HA, Dillingham EM, Prudic J, Cooper T, McCall WV, Rosenquist P, et al. Effect of concomitant pharmacotherapy on electroconvulsive therapy outcomes: short-term efficacy and adverse effects. *Arch Gen Psychiatry.* 2009 Jul;66(7):729-37.
1080. Sackeim HA, Freeman J, McElhiney M, Coleman E, Prudic J, Devanand DP. Effects of major depression on estimates of intelligence. *J Clin Exp Neuropsychol.* 1992 Mar;14(2):268-88.
1081. Sackeim HA, Haskett RF, Mulsant BH, Thase ME, Mann JJ, Pettinati HM, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *Jama.* 2001 Mar 14;285(10):1299-307.
1082. Sackeim HA, Keilp JG, Rush AJ, George MS, Marangell LB, Dormer JS, et al. The effects of vagus nerve stimulation on cognitive performance in patients with treatment-resistant depression. *Neuropsychiatry Neuropsychol Behav Neurol.* 2001 Jan;14(1):53-62.
1083. Sackeim HA, Lubner B, Katzman GP, Moeller JR, Prudic J, Devanand DP, et al. The effects of electroconvulsive therapy on quantitative electroencephalograms. Relationship to clinical outcome. *Arch Gen Psychiatry.* 1996 Sep;53(9):814-24.
1084. Sackeim HA, Lubner B, Moeller JR, Prudic J, Devanand DP, Nobler MS. Electrophysiological correlates of the adverse cognitive effects of electroconvulsive therapy. *J Ect.* 2000 Jun;16(2):110-20.

1085. Sackeim HA, Prudic J, Devanand DP, Decina P, Kerr B, Malitz S. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. *J Clin Psychopharmacol*. 1990 Apr;10(2):96-104.
1086. Sackeim HA, Prudic J, Devanand DP, Kiersky JE, Fitzsimons L, Moody BJ, et al. Effects of stimulus intensity and electrode placement on the efficacy and cognitive effects of electroconvulsive therapy. *N Engl J Med*. 1993 Mar 25;328(12):839-46.
1087. Sackeim HA, Prudic J, Fuller R, Keilp J, Lavori PW, Olfson M. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology*. 2007 Jan;32(1):244-54.
1088. Sackeim HA, Rush AJ, George MS, Marangell LB, Husain MM, Nahas Z, et al. Vagus nerve stimulation (VNS) for treatment-resistant depression: efficacy, side effects, and predictors of outcome. *Neuropsychopharmacology*. 2001 Nov;25(5):713-28.
1089. Sagud M, Mihaljevic-Peles A, Muck-Seler D, Jakovljevic M, Pivac N. Quetiapine augmentation in treatment-resistant depression: a naturalistic study. *Psychopharmacology (Berl)*. 2006 Sep;187(4):511-4.
1090. Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, et al. Electroconvulsive therapy decreases dopamine D2 receptor binding in the anterior cingulate in patients with depression: a controlled study using positron emission tomography with radioligand [¹¹C]FLB 457. *J Clin Psychiatry*. 2010 Jun;71(6):793-9.
1091. Saito S, Nishihara F, Akihiro T, Nishikawa K, Obata H, Goto F, et al. Landiolol and esmolol prevent tachycardia without altering cerebral blood flow. *Can J Anaesth*. 2005 Dec;52(10):1027-34.
1092. Saiz-Ruiz J, Ibanez A, Diaz-Marsa M, Arias F, Padin J, Martin-Carrasco M, et al. Efficacy of venlafaxine in major depression resistant to selective serotonin reuptake inhibitors. *Prog Neuropsychopharmacol Biol Psychiatry*. 2002 Oct;26(6):1129-34.
1093. Sajatovic M, DiGiovanni S, Fuller M, Belton J, DeVega E, Marqua S, et al. Nefazodone therapy in patients with treatment-resistant or treatment-intolerant depression and high psychiatric comorbidity. *Clin Ther*. 1999 Apr;21(4):733-40.
1094. Sakamoto A, Ogawa R, Suzuki H, Kimura M, Okubo Y, Fujiya T. Landiolol attenuates acute hemodynamic responses but does not reduce seizure duration during maintenance electroconvulsive therapy. *Psychiatry Clin Neurosci*. 2004 Dec;58(6):630-5.
1095. Salazar MR. Alpha lipoic acid: a novel treatment for depression. *Med Hypotheses*. 2000 Dec;55(6):510-2.
1096. Sanacora G, Fenton LR, Fasula MK, Rothman DL, Levin Y, Krystal JH, et al. Cortical gamma-aminobutyric acid concentrations in depressed patients receiving cognitive behavioral therapy. *Biol Psychiatry*. 2006 Feb 1;59(3):284-6.
1097. Sanacora G, Kendell SF, Levin Y, Simen AA, Fenton LR, Coric V, et al. Preliminary evidence of riluzole efficacy in antidepressant-treated patients with residual depressive symptoms. *Biol Psychiatry*. 2007 Mar 15;61(6):822-5.
1098. Sanacora G, Mason GF, Rothman DL, Hyder F, Ciarcia JJ, Ostroff RB, et al. Increased cortical GABA concentrations in depressed patients receiving ECT. *Am J Psychiatry*. 2003 Mar;160(3):577-9.
1099. Saravanan ES, Gangadhar BN, Janakiramaiah N, Pandey RS, Murthy HS, Subbakrishna DK. Does higher cardiovascular response to ECT predict early antidepressant effect? *J Affect Disord*. 2002 May;69(1-3):101-8.
1100. Sartorius A, Henn FA. Deep brain stimulation of the lateral habenula in treatment resistant major depression. *Med Hypotheses*. 2007;69(6):1305-8.
1101. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. *J Clin Psychiatry*. 1989 Jul;50(7):241-9.

1102. Sato Y, Yasui-Furukori N, Nakagami T, Saito M, Kaneko S. Augmentation of antidepressants with perospirone for treatment-resistant major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2009 Apr 30;33(3):416-8.
1103. Sawabini KA, Watts RL. Treatment of depression in Parkinson's disease. *Parkinsonism Relat Disord*. 2004 May;10 Suppl 1:S37-41.
1104. Sawayama E, Takahashi M, Inoue A, Nakajima K, Kano A, Sawayama T, et al. Moderate hyperventilation prolongs electroencephalogram seizure duration of the first electroconvulsive therapy. *J Ect*. 2008 Sep;24(3):195-8.
1105. Schachter SC. Vagus nerve stimulation: mood and cognitive effects. *Epilepsy Behav*. 2004 Feb;5 Suppl 1:S56-9.
1106. Schat A, van den Broek WW, Mulder PG, Birkenhager TK, van Tuijl R, Murre JM. Changes in everyday and semantic memory function after electroconvulsive therapy for unipolar depression. *J Ect*. 2007 Sep;23(3):153-7.
1107. Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. *NeuroRx*. 2005 Oct;2(4):590-611.
1108. Schelde JT. Incomplete recovery among endogenously depressed patients: an ethological analysis. *J Nerv Ment Dis*. 2000 Jun;188(6):372-6.
1109. Schiffer F, Glass I, Lord J, Teicher MH. Prediction of clinical outcomes from rTMS in depressed patients with lateral visual field stimulation: a replication. *J Neuropsychiatry Clin Neurosci*. 2008 Spring;20(2):194-200.
1110. Schindler F, Angheliescu IG. Lithium versus lamotrigine augmentation in treatment resistant unipolar depression: a randomized, open-label study. *Int Clin Psychopharmacol*. 2007 May;22(3):179-82.
1111. Schlaepfer TE, Frick C, Zobel A, Maier W, Heuser I, Bajbouj M, et al. Vagus nerve stimulation for depression: efficacy and safety in a European study. *Psychol Med*. 2008 May;38(5):651-61.
1112. Schmauss M, Kapfhammer HP, Meyr P, Hoff P. Combined MAO-inhibitor and tri-(tetra) cyclic antidepressant treatment in therapy resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry*. 1988;12(4):523-32.
1113. Schmauss M, Laakmann G, Dieterle D. Effects of alpha 2-receptor blockade in addition to tricyclic antidepressants in therapy-resistant depression. *J Clin Psychopharmacol*. 1988 Apr;8(2):108-11.
1114. Schopf J. Treatment of depressions resistant to tricyclic antidepressants, related drugs or MAO-inhibitors by lithium addition: review of the literature. *Pharmacopsychiatry*. 1989 Sep;22(5):174-82.
1115. Schopf J, Baumann P, Lemarchand T, Rey M. Treatment of endogenous depressions resistant to tricyclic antidepressants or related drugs by lithium addition. Results of a placebo-controlled double-blind study. *Pharmacopsychiatry*. 1989 Sep;22(5):183-7.
1116. Schopf J, Lemarchand T. Lithium addition in endogenous depressions resistant to tricyclic antidepressants or related drugs: relation to the status of the pituitary-thyroid axis. *Pharmacopsychiatry*. 1994 Sep;27(5):198-201.
1117. Schule C, Baghai TC, Eser D, Hecht S, Hermisson I, Born C, et al. Mirtazapine monotherapy versus combination therapy with mirtazapine and aripiprazole in depressed patients without psychotic features: a 4-week open-label parallel-group study. *World J Biol Psychiatry*. 2007;8(2):112-22.
1118. Schule C, Zwanzger P, Baghai T, Mikhael P, Thoma H, Moller HJ, et al. Effects of antidepressant pharmacotherapy after repetitive transcranial magnetic stimulation in major depression: an open follow-up study. *J Psychiatr Res*. 2003 Mar-Apr;37(2):145-53.
1119. Schultz SK, Anderson EA, van de Borne P. Heart rate variability before and after treatment with electroconvulsive therapy. *J Affect Disord*. 1997 Jun;44(1):13-20.

1120. Schulze-Rauschenbach SC, Harms U, Schlaepfer TE, Maier W, Falkai P, Wagner M. Distinctive neurocognitive effects of repetitive transcranial magnetic stimulation and electroconvulsive therapy in major depression. *Br J Psychiatry*. 2005 May;186:410-6.
1121. Schuster P, Opgenoorth E, Gabriel E, Presslich O, Sowinetz B. Results of learning experiments in the course of treatment of endogenomorphic depression. A comparison of electroconvulsive and pharmacological treatment. *Psychopathology*. 1986;19(3):116-30.
1122. Schutter DJ. Antidepressant efficacy of high-frequency transcranial magnetic stimulation over the left dorsolateral prefrontal cortex in double-blind sham-controlled designs: a meta-analysis. *Psychol Med*. 2009 Jan;39(1):65-75.
1123. Schweitzer I, Burrows G, Tuckwell V, Polonowita A, Flynn P, George T, et al. Sustained response to open-label venlafaxine in drug-resistant major depression. *J Clin Psychopharmacol*. 2001 Apr;21(2):185-9.
1124. Schweitzer I, Tuckwell V, Johnson G. A review of the use of augmentation therapy for the treatment of resistant depression: implications for the clinician. *Aust N Z J Psychiatry*. 1997 Jun;31(3):340-52.
1125. Scott AI, Boddy H. The effect of repeated bilateral electroconvulsive therapy on seizure threshold. *J Ect*. 2000 Sep;16(3):244-51.
1126. Scott AI, Rodger CR, Stocks RH, Shering AP. Is old-fashioned electroconvulsive therapy more efficacious? A randomised comparative study of bilateral brief-pulse and bilateral sine-wave treatments. *Br J Psychiatry*. 1992 Mar;160:360-4.
1127. Scott AI, Whalley LJ, Legros JJ. Treatment outcome, seizure duration, and the neurophysin response to ECT. *Biol Psychiatry*. 1989 Mar 1;25(5):585-97.
1128. Scott J, Eccleston D, Boys R. Can we predict the persistence of depression? *Br J Psychiatry*. 1992 Nov;161:633-7.
1129. Scott J, Palmer S, Paykel E, Teasdale J, Hayhurst H. Use of cognitive therapy for relapse prevention in chronic depression. Cost-effectiveness study. *Br J Psychiatry* 2003;221-7.
1130. Scott TF, Allen D, Price TR, McConnell H, Lang D. Characterization of major depression symptoms in multiple sclerosis patients. *J Neuropsychiatry Clin Neurosci*. 1996 Summer;8(3):318-23.
1131. Seemuller F, Riedel M, Obermeier M, Bauer M, Adli M, Kronmuller K, et al. Outcomes of 1014 naturalistically treated inpatients with major depressive episode. *Eur Neuropsychopharmacol*. 2010 May;20(5):346-55.
1132. Segman RH, Shapira B, Gorfine M, Lerer B. Onset and time course of antidepressant action: psychopharmacological implications of a controlled trial of electroconvulsive therapy. *Psychopharmacology (Berl)*. 1995 Jun;119(4):440-8.
1133. Seminowicz DA, Mayberg HS, McIntosh AR, Goldapple K, Kennedy S, Segal Z, et al. Limbic-frontal circuitry in major depression: a path modeling metanalysis. *Neuroimage*. 2004 May;22(1):409-18.
1134. Sensky T, Turkington D, Kingdon D, Scott JL, Scott J, Siddler R, et al. A randomized controlled trial of cognitive-behavioral therapy for persistent symptoms in schizophrenia resistant to medication. *Arch Gen Psychiatry*. 2000 Feb;57(2):165-72.
1135. Serretti A, Calati R, Massat I, Linotte S, Kasper S, Lecrubier Y, et al. Cytochrome P450 CYP1A2, CYP2C9, CYP2C19 and CYP2D6 genes are not associated with response and remission in a sample of depressive patients. *Int Clin Psychopharmacol*. 2009 Sep;24(5):250-6.
1136. Shah N, Mahadeshwar S, Bhakta S, Bhirud M, Fernandes P, Andrade C. The safety and efficacy of benzodiazepine-modified treatments as a special form of unmodified ECT. *J ECT*. 2010 Mar;26(1):23-9.
1137. Shajahan PM, Glabus MF, Gooding PA, Shah PJ, Ebmeier KP. Reduced cortical excitability in depression. Impaired post-exercise motor facilitation with transcranial magnetic stimulation. *Br J Psychiatry*. 1999 May;174:449-54.

1138. Shapira B, Cohen J, Newman ME, Lerer B. Prolactin response to fenfluramine and placebo challenge following maintenance pharmacotherapy withdrawal in remitted depressed patients. *Biol Psychiatry*. 1993 Apr 1;33(7):531-5.
1139. Shapira B, Gorfine M, Lerer B. A prospective study of lithium continuation therapy in depressed patients who have responded to electroconvulsive therapy. *Convuls Ther*. 1995 Jun;11(2):80-5.
1140. Shapira B, Lerer B. Speed of response to bilateral ECT: an examination of possible predictors in two controlled trials. *J Ect*. 1999 Sep;15(3):202-6.
1141. Shapira B, Lerer B, Kindler S, Lichtenberg P, Gropp C, Cooper T, et al. Enhanced serotonergic responsivity following electroconvulsive therapy in patients with major depression. *Br J Psychiatry*. 1992 Feb;160:223-9.
1142. Shapira B, Lidsky D, Gorfine M, Lerer B. Electroconvulsive therapy and resistant depression: clinical implications of seizure threshold. *J Clin Psychiatry*. 1996 Jan;57(1):32-8.
1143. Shapira B, Nemets B, Trachtenberg A, Belmaker RH. Phenytoin as an augmentation for SSRI failures: a small controlled study. *J Affect Disord*. 2006 Nov;96(1-2):123-6.
1144. Shapira B, Oppenheim G, Zohar J, Segal M, Malach D, Belmaker RH. Lack of efficacy of estrogen supplementation to imipramine in resistant female depressives. *Biol Psychiatry*. 1985 May;20(5):576-9.
1145. Shapira B, Tubi N, Drexler H, Lidsky D, Calev A, Lerer B. Cost and benefit in the choice of ECT schedule. Twice versus three times weekly ECT. *Br J Psychiatry*. 1998 Jan;172:44-8.
1146. Shapira B, Tubi N, Lerer B. Balancing speed of response to ECT in major depression and adverse cognitive effects: role of treatment schedule. *J Ect*. 2000 Jun;16(2):97-109.
1147. Sharma R, Hedeker D, Pandey G, Janicak P, Davis J. A longitudinal study of plasma cortisol and depressive symptomatology by random regression analysis. *Biol Psychiatry*. 1992 Feb 1;31(3):304-14.
1148. Sharma V. Treatment resistance in unipolar depression: Is it an iatrogenic phenomenon caused by antidepressant treatment of patients with a bipolar diathesis? *Med Hypotheses*. 2006;67(5):1142-5.
1149. Sharma V, Khan M, Smith A. A closer look at treatment resistant depression: is it due to a bipolar diathesis? *J Affect Disord*. 2005 Feb;84(2-3):251-7.
1150. Sharma V, Mazmanian D, Persad E, Kueneman K. A comparison of comorbid patterns in treatment-resistant unipolar and bipolar depression. *Can J Psychiatry*. 1995 Jun;40(5):270-4.
1151. Sharpley AL, Bhagwagar Z, Hafizi S, Whale WR, Gijnsman HJ, Cowen PJ. Risperidone augmentation decreases rapid eye movement sleep and decreases wake in treatment-resistant depressed patients. *J Clin Psychiatry*. 2003 Feb;64(2):192-6.
1152. Shavitt RG, Valerio C, Fossaluza V, da Silva EM, Cordeiro Q, Diniz JB, et al. The impact of trauma and post-traumatic stress disorder on the treatment response of patients with obsessive-compulsive disorder. *Eur Arch Psychiatry Clin Neurosci*. 2010 Mar;260(2):91-9.
1153. Shaw DM. Pharmacological management of treatment-resistant depression. *Psychopharmacol Ser*. 1988;5:118-29.
1154. Shelton RC. Mood-stabilizing drugs in depression. *J Clin Psychiatry*. 1999;60 Suppl 5:37-40; discussion 1-2.
1155. Shelton RC. Treatment options for refractory depression. *J Clin Psychiatry*. 1999;60 Suppl 4:57-61; discussion 2-3.
1156. Shelton RC. The use of antidepressants in novel combination therapies. *J Clin Psychiatry*. 2003;64 Suppl 2:14-8.
1157. Shelton RC, Papakostas GI. Augmentation of antidepressants with atypical antipsychotics for treatment-resistant major depressive disorder. *Acta Psychiatr Scand*. 2008 Apr;117(4):253-9.
1158. Shelton RC, Tollefson GD, Tohen M, Stahl S, Gannon KS, Jacobs TG, et al. A novel augmentation strategy for treating resistant major depression. *Am J Psychiatry*. 2001;131-4.

1159. Shelton RC, Williamson DJ, Corya SA, Sanger TM, Van Campen LE, Case M, et al. Olanzapine/fluoxetine combination for treatment-resistant depression: a controlled study of SSRI and nortriptyline resistance. *J Clin Psychiatry* 2005;1289-97.
1160. Shergill SS, Katona CL. Pharmacological choices after one antidepressant fails: a survey of UK psychiatrists. *J Affect Disord*. 1997 Mar;43(1):19-25.
1161. Shiah IS, Yatham LN, Srisurapanont M, Lam RW, Tam EM, Zis AP. Does the addition of pindolol accelerate the response to electroconvulsive therapy in patients with major depression? A double-blind, placebo-controlled pilot study. *J Clin Psychopharmacol*. 2000 Jun;20(3):373-8.
1162. Shirayama T, Sakamoto T, Sakatani T, Mani H, Yamamoto T, Matsubara H. Usefulness of paroxetine in depressed men with paroxysmal atrial fibrillation. *Am J Cardiol*. 2006 Jun 15;97(12):1749-51.
1163. Shulman KI, Fischer HD, Herrmann N, Huo CY, Anderson GM, Rochon PA. Current prescription patterns and safety profile of irreversible monoamine oxidase inhibitors: a population-based cohort study of older adults. *J Clin Psychiatry*. 2009 Dec;70(12):1681-6.
1164. Sienaert P, Vansteelandt K, Demyttenaere K, Peuskens J. Randomized comparison of ultra-brief bifrontal and unilateral electroconvulsive therapy for major depression: cognitive side-effects. *J Affect Disord*. 2010 Apr;122(1-2):60-7.
1165. Sienaert PA, Vansteelandt K, Demyttenaere K, Peuskens J. Predictors of patient satisfaction after ultrabrief bifrontal and unilateral electroconvulsive therapies for major depression. *J ECT*. 2010 Mar;26(1):55-9.
1166. Silfverskiold P, Risberg J. Regional cerebral blood flow in depression and mania. *Arch Gen Psychiatry*. 1989 Mar;46(3):253-9.
1167. Silfverskiold P, Rosen I, Risberg J. Effects of electroconvulsive therapy on EEG and cerebral blood flow in depression. *Eur Arch Psychiatry Neurol Sci*. 1987;236(4):202-8.
1168. Simon JS, Nemeroff CB. Aripiprazole augmentation of antidepressants for the treatment of partially responding and nonresponding patients with major depressive disorder. *J Clin Psychiatry*. 2005 Oct;66(10):1216-20.
1169. Simpson GM, El Sheshai A, Rady A, Kingsbury SJ, Fayek M. Sertraline as monotherapy in the treatment of psychotic and nonpsychotic depression. *J Clin Psychiatry*. 2003 Aug;64(8):959-65.
1170. Simpson S, Baldwin RC, Jackson A, Burns A. The differentiation of DSM-III-R psychotic depression in later life from nonpsychotic depression: comparisons of brain changes measured by multispectral analysis of magnetic resonance brain images, neuropsychological findings, and clinical features. *Biol Psychiatry*. 1999 Jan 15;45(2):193-204.
1171. Simpson S, Baldwin RC, Jackson A, Burns AS. Is subcortical disease associated with a poor response to antidepressants? Neurological, neuropsychological and neuroradiological findings in late-life depression. *Psychol Med*. 1998 Sep;28(5):1015-26.
1172. Sit D, Perel JM, Luther JF, Wisniewski SR, Helsel JC, Wisner KL. Disposition of chiral and racemic fluoxetine and norfluoxetine across childbearing. *J Clin Psychopharmacol*. 2010 Aug;30(4):381-6.
1173. Skolnick P, Popik P, Trullas R. Glutamate-based antidepressants: 20 years on. *Trends Pharmacol Sci*. 2009 Nov;30(11):563-9.
1174. Slotkin TA, Hays JC, Nemeroff CB, Carroll BJ. Dexamethasone suppression test identifies a subset of elderly depressed patients with reduced platelet serotonin transport and resistance to imipramine inhibition of transport. *Depress Anxiety*. 1997;6(1):19-25.
1175. Sluzewska A, Sobieska M, Rybakowski JK. Changes in acute-phase proteins during lithium potentiation of antidepressants in refractory depression. *Neuropsychobiology*. 1997;35(3):123-7.
1176. Small JG, Kellams JJ, Dennis JL, Milstein V. Comparison of molindone and tranlycypromine in the treatment of refractory depression. *J Clin Pharmacol*. 1981 Aug-Sep;21(8-9):351-8.

1177. Small JG, Small IF. Electroconvulsive therapy update. *Psychopharmacol Bull.* 1981 Oct;17(4):29-42.
1178. Smith DJ, Harrison N, Muir W, Blackwood DH. The high prevalence of bipolar spectrum disorders in young adults with recurrent depression: toward an innovative diagnostic framework. *J Affect Disord.* 2005 Feb;84(2-3):167-78.
1179. Smith GE, Rasmussen KG, Jr., Cullum CM, Felmlee-Devine MD, Petrides G, Rummans TA, et al. A randomized controlled trial comparing the memory effects of continuation electroconvulsive therapy versus continuation pharmacotherapy: results from the Consortium for Research in ECT (CORE) study. *J Clin Psychiatry.* 2010 Feb;71(2):185-93.
1180. Smith M, Vogler J, Zarrouf F, Sheaves C, Jesse J. Electroconvulsive therapy: the struggles in the decision-making process and the aftermath of treatment. *Issues Ment Health Nurs.* 2009 Sep;30(9):554-9.
1181. Sneed JR, Roose SP, Keilp JG, Krishnan KR, Alexopoulos GS, Sackeim HA. Response inhibition predicts poor antidepressant treatment response in very old depressed patients. *Am J Geriatr Psychiatry.* 2007 Jul;15(7):553-63.
1182. Sobin C, Prudic J, Devanand DP, Nobler MS, Sackeim HA. Who responds to electroconvulsive therapy? A comparison of effective and ineffective forms of treatment. *Br J Psychiatry.* 1996 Sep;169(3):322-8.
1183. Sobin C, Sackeim HA, Prudic J, Devanand DP, Moody BJ, McElhiney MC. Predictors of retrograde amnesia following ECT. *Am J Psychiatry.* 1995 Jul;152(7):995-1001.
1184. Sokolski KN, Conney JC, Brown BJ, DeMet EM. Once-daily high-dose pindolol for SSRI-refractory depression. *Psychiatry Res.* 2004 Feb 15;125(2):81-6.
1185. Solomon DA, Keller MB, Leon AC, Mueller TI, Lavori PW, Shea MT, et al. Multiple recurrences of major depressive disorder. *Am J Psychiatry.* 2000 Feb;157(2):229-33.
1186. Sommer BR, Satlin A, Friedman L, Cole JO. Glycopyrrolate versus atropine in post-ECT amnesia in the elderly. *J Geriatr Psychiatry Neurol.* 1989 Jan-Mar;2(1):18-21.
1187. Sonawalla SB, Fava M. Severe depression: is there a best approach? *CNS Drugs.* 2001;15(10):765-76.
1188. Souery D, Amsterdam J, de Montigny C, Lecrubier Y, Montgomery S, Lipp O, et al. Treatment resistant depression: methodological overview and operational criteria. *Eur Neuropsychopharmacol.* 1999 Jan;9(1-2):83-91.
1189. Souery D, Oswald P, Massat I, Bailer U, Bollen J, Demyttenaere K, et al. Clinical factors associated with treatment resistance in major depressive disorder: results from a European multicenter study. *J Clin Psychiatry.* 2007 Jul;68(7):1062-70.
1190. Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry.* 2006;67 Suppl 6:16-22.
1191. Souery D, Van der Auwera K. The multiple facets of treatment-resistant depression. *CNS Spectr.* 2004 Nov;9(11):803-7.
1192. Spalletta G, Guida G, Caltagirone C. Is left stroke a risk-factor for selective serotonin reuptake inhibitor antidepressant treatment resistance? *J Neurol.* 2003 Apr;250(4):449-55.
1193. Speer AM, Repella JD, Figueras S, Demian NK, Kimbrell TA, Wasserman EM, et al. Lack of adverse cognitive effects of 1 Hz and 20 Hz repetitive transcranial magnetic stimulation at 100% of motor threshold over left prefrontal cortex in depression. *J Ect.* 2001 Dec;17(4):259-63.
1194. Sperling W, Reulbach U, Kornhuber J. Clinical benefits and cost effectiveness of vagus nerve stimulation in a long-term treatment of patients with major depression. *Pharmacopsychiatry.* 2009 May;42(3):85-8.
1195. Spijker J, Nolen WA. An algorithm for the pharmacological treatment of depression. *Acta Psychiatr Scand.* 2010 Mar;121(3):180-9.
1196. Spronk D, Arns M, Bootsma A, van Ruth R, Fitzgerald PB. Long-term effects of left frontal rTMS on EEG and ERPs in patients with depression. *Clin EEG Neurosci.* 2008 Jul;39(3):118-24.

1197. Squire LR, Slater PC. Electroconvulsive therapy and complaints of memory dysfunction: a prospective three-year follow-up study. *Br J Psychiatry*. 1983 Jan;142:1-8.
1198. St John D. Pharmacotherapeutic approaches to treatment-resistant depression. *Jaapa*. 2003 Mar;16(3):32-4, 7-8, 40 passim.
1199. Stain-Malmgren R, Khoury AE, Aberg-Wistedt A, Tham A. Serotonergic function in major depression and effect of sertraline and paroxetine treatment. *Int Clin Psychopharmacol*. 2001 Mar;16(2):93-101.
1200. Standish-Barry H. Treating refractory depression. *Int Clin Psychopharmacol*. 1990 Jul;5 Suppl 3:33-43.
1201. Staroverov AT, Zhukov OB, Raigorodskii YM. Efficacy of transcranial magnetotherapy in the complex treatment of alcohol withdrawal syndrome. *Neurosci Behav Physiol*. 2009 Nov;39(9):891-5.
1202. Steen A, Den Boer JA. A double-blind six months comparative study of milnacipran and clomipramine in major depressive disorder. *Int Clin Psychopharmacol*. 1997 Sep;12(5):269-81.
1203. Steffens DC, McQuoid DR, Krishnan KR. The Duke Somatic Treatment Algorithm for Geriatric Depression (STAGED) approach. *Psychopharmacol Bull*. 2002 Spring;36(2):58-68.
1204. Steffens DC, Pieper CF, Bosworth HB, MacFall JR, Provenzale JM, Payne ME, et al. Biological and social predictors of long-term geriatric depression outcome. *Int Psychogeriatr*. 2005 Mar;17(1):41-56.
1205. Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. *Am J Psychiatry*. 2002 Oct;159(10):1777-9.
1206. Stek ML, Van der Wurff FB, Hoogendijk WL, Beekman AT. Electroconvulsive therapy for the depressed elderly. *Cochrane Database Syst Rev*. 2003(2):CD003593.
1207. Stek ML, Van Exel E, Van Tilburg W, Westendorp RG, Beekman AT. The prognosis of depression in old age: outcome six to eight years after clinical treatment. *Aging Ment Health*. 2002 Aug;6(3):282-5.
1208. Stern RA, Nevels CT, Shelhorse ME, Prohaska ML, Mason GA, Prange AJ, Jr. Antidepressant and memory effects of combined thyroid hormone treatment and electroconvulsive therapy: preliminary findings. *Biol Psychiatry*. 1991 Sep 15;30(6):623-7.
1209. Stern SL, Mendels J. Drug combinations in the treatment of refractory depression: a review. *J Clin Psychiatry*. 1981 Oct;42(10):368-73.
1210. Stern WC, Harto-Truax N, Bauer N. Efficacy of bupropion in tricyclic-resistant or intolerant patients. *J Clin Psychiatry*. 1983 May;44(5 Pt 2):148-52.
1211. Stewart JW, McGrath PJ, Quitkin FM. Do age of onset and course of illness predict different treatment outcome among DSM IV depressive disorders with atypical features? *Neuropsychopharmacology*. 2002 Feb;26(2):237-45.
1212. Stiebel VG. Maintenance electroconvulsive therapy for chronic mentally ill patients: a case series. *Psychiatr Serv*. 1995 Mar;46(3):265-8.
1213. Stoppe A, Louza M, Rosa M, Gil G, Rigonatti S. Fixed high-dose electroconvulsive therapy in the elderly with depression: a double-blind, randomized comparison of efficacy and tolerability between unilateral and bilateral electrode placement. *J Ect*. 2006 Jun;22(2):92-9.
1214. Stoudemire A. Expanding psychopharmacologic treatment options for the depressed medical patient. *Psychosomatics*. 1995 Mar-Apr;36(2):S19-26.
1215. Stoudemire A, Hill CD, Dalton ST, Marquardt MG. Rehospitalization rates in older depressed adults after antidepressant and electroconvulsive therapy treatment. *J Am Geriatr Soc*. 1994 Dec;42(12):1282-5.
1216. Stoudemire A, Hill CD, Marquardt M, Dalton S, Lewison BJ. Recovery and relapse in geriatric depression after treatment with antidepressants and ECT in a medical-psychiatric population. *Gen Hosp Psychiatry*. 1998 May;20(3):170-4.

1217. Stoudemire A, Hill CD, Morris R, Lewison BJ. Long-term outcome of treatment-resistant depression in older adults. *Am J Psychiatry*. 1993 Oct;150(10):1539-40.
1218. Stoudemire A, Hill CD, Morris R, Martino-Saltzman D, Lewison B. Long-term affective and cognitive outcome in depressed older adults. *Am J Psychiatry*. 1993 Jun;150(6):896-900.
1219. Stoudemire A, Hill CD, Morris R, Martino-Saltzman D, Markwalter H, Lewison B. Cognitive outcome following tricyclic and electroconvulsive treatment of major depression in the elderly. *Am J Psychiatry*. 1991 Oct;148(10):1336-40.
1220. Stoudemire A, Knos G, Gladson M, Markwalter H, Sung YF, Morris R, et al. Labetalol in the control of cardiovascular responses to electroconvulsive therapy in high-risk depressed medical patients. *J Clin Psychiatry*. 1990 Dec;51(12):508-12.
1221. Strunk DR, Stewart MO, Hollon SD, DeRubeis RJ, Fawcett J, Amsterdam JD, et al. Can pharmacotherapists be too supportive? A process study of active medication and placebo in the treatment of depression. *Psychol Med*. 2010 Aug;40(8):1379-87.
1222. Stryjer R, Strous RD, Shaked G, Bar F, Feldman B, Kotler M, et al. Amantadine as augmentation therapy in the management of treatment-resistant depression. *Int Clin Psychopharmacol*. 2003 Mar;18(2):93-6.
1223. Sunderland T, Cohen RM, Molchan S, Lawlor BA, Mellow AM, Newhouse PA, et al. High-dose selegiline in treatment-resistant older depressive patients. *Arch Gen Psychiatry*. 1994/08/01 ed 1994:607-15.
1224. Suominen KH, Isometsa ET, Henriksson MM, Ostamo AI, Lonnqvist JK. Inadequate treatment for major depression both before and after attempted suicide. *Am J Psychiatry*. 1998 Dec;155(12):1778-80.
1225. Surtees PG, Barkley C. Future imperfect: the long-term outcome of depression. *Br J Psychiatry*. 1994 Mar;164(3):327-41.
1226. Swan J, Sorrell E, MacVicar B, Durham R, Matthews K. "Coping with depression": an open study of the efficacy of a group psychoeducational intervention in chronic, treatment-refractory depression. *J Affect Disord*. 2004 Oct 1;82(1):125-9.
1227. Swartz CM, Morrow V, Surles L, James JF. Long-term outcome after ECT for catatonic depression. *J Ect*. 2001 Sep;17(3):180-3.
1228. Swoboda E, Conca A, Konig P, Waanders R, Hansen M. Maintenance electroconvulsive therapy in affective and schizoaffective disorder. *Neuropsychobiology*. 2001 Jan;43(1):23-8.
1229. Szuba MP, O'Reardon JP, Rai AS, Snyder-Kastenberg J, Amsterdam JD, Gettes DR, et al. Acute mood and thyroid stimulating hormone effects of transcranial magnetic stimulation in major depression. *Biol Psychiatry*. 2001 Jul 1;50(1):22-7.
1230. Tajima O. Japanese experience with dual-action antidepressants. *Int Clin Psychopharmacol*. 2002 Jun;17 Suppl 1:S37-42.
1231. Takahashi H, Kamata M, Yoshida K, Higuchi H, Ishigooka J. Augmentation with olanzapine in TCA-refractory depression with melancholic features: a consecutive case series. *Hum Psychopharmacol*. 2008 Apr;23(3):217-20.
1232. Takahashi S, Mizukami K, Yasuno F, Asada T. Depression associated with dementia with Lewy bodies (DLB) and the effect of somatotherapy. *Psychogeriatrics*. 2009/07/17 ed 2009:56-61.
1233. Talbot NL, Conwell Y, O'Hara MW, Stuart S, Ward EA, Gamble SA, et al. Interpersonal psychotherapy for depressed women with sexual abuse histories: a pilot study in a community mental health center. *J Nerv Ment Dis*. 2005 Dec;193(12):847-50.
1234. Tam W, Young JP, John G, Lader MH. A controlled comparison of flupenthixol decanoate injections and oral amitriptyline in depressed out-patients. *Br J Psychiatry*. 1982 Mar;140:287-91.
1235. Tang WK, Ungvari GS, Leung HC. Effect of piracetam on ECT-induced cognitive disturbances: a randomized, placebo-controlled, double-blind study. *J Ect*. 2002 Sep;18(3):130-7.

1236. Tanum LH. Combination treatment with antidepressants in refractory depression. *Int Clin Psychopharmacol.* 1994 Jun;9 Suppl 2:37-40.
1237. Targum SD, Greenberg RD, Harmon RL, Kessler K, Salerian AJ, Fram DH. Thyroid hormone and the TRH stimulation test in refractory depression. *J Clin Psychiatry.* 1984 Aug;45(8):345-6.
1238. Taylor D. Selective serotonin reuptake inhibitors and tricyclic antidepressants in combination. Interactions and therapeutic uses. *Br J Psychiatry.* 1995 Nov;167(5):575-80.
1239. Taylor SM. Electroconvulsive therapy, brain-derived neurotrophic factor, and possible neurorestorative benefit of the clinical application of electroconvulsive therapy. *J Ect.* 2008 Jun;24(2):160-5.
1240. Tedlow J, Fava M, Uebelacker L, Nierenberg AA, Alpert JE, Rosenbaum J. Outcome definitions and predictors in depression. *Psychother Psychosom.* 1998 Jul-Oct;67(4-5):266-70.
1241. Telner JI, Singhal RL. Psychiatric progress. The learned helplessness model of depression. *J Psychiatr Res.* 1984;18(3):207-15.
1242. Tew JD, Jr., Mulsant BH, Haskett RF, Dolata D, Hixson L, Mann JJ. A randomized comparison of high-charge right unilateral electroconvulsive therapy and bilateral electroconvulsive therapy in older depressed patients who failed to respond to 5 to 8 moderate-charge right unilateral treatments. *J Clin Psychiatry.* 2002 Dec;63(12):1102-5.
1243. Tew JD, Jr., Mulsant BH, Haskett RF, Joan P, Begley AE, Sackeim HA. Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. *Ann Clin Psychiatry.* 2007 Jan-Mar;19(1):1-4.
1244. Tew JD, Jr., Mulsant BH, Haskett RF, Prudic J, Thase ME, Crowe RR, et al. Acute efficacy of ECT in the treatment of major depression in the old-old. *Am J Psychiatry.* 1999 Dec;156(12):1865-70.
1245. Tew JD, Jr., Mulsant BH, Houck PR, Lenze EJ, Whyte EM, Miller MD, et al. Impact of prior treatment exposure on response to antidepressant treatment in late life. *Am J Geriatr Psychiatry.* 2006 Nov;14(11):957-65.
1246. Thase ME. Long-term treatments of recurrent depressive disorders. *J Clin Psychiatry.* 1992 Sep;53 Suppl:32-44.
1247. Thase ME. The role of Axis II comorbidity in the management of patients with treatment-resistant depression. *Psychiatr Clin North Am.* 1996 Jun;19(2):287-309.
1248. Thase ME. Psychotherapy of refractory depressions. *Depress Anxiety.* 1997;5(4):190-201.
1249. Thase ME. The need for clinically relevant research on treatment-resistant depression. *J Clin Psychiatry.* 2001 Apr;62(4):221-4.
1250. Thase ME. What role do atypical antipsychotic drugs have in treatment-resistant depression? *J Clin Psychiatry.* 2002 Feb;63(2):95-103.
1251. Thase ME. New approaches to managing difficult-to-treat depressions. *J Clin Psychiatry.* 2003;64 Suppl 1:3-4.
1252. Thase ME. Therapeutic alternatives for difficult-to-treat depression: a narrative review of the state of the evidence. *CNS Spectr.* 2004 Nov;9(11):808-16, 18-21.
1253. Thase ME. Bipolar depression: issues in diagnosis and treatment. *Harv Rev Psychiatry.* 2005 Sep-Oct;13(5):257-71.
1254. Thase ME. Management of patients with treatment-resistant depression. *J Clin Psychiatry.* 2008 Mar;69(3):e8.
1255. Thase ME. Pharmacotherapeutic treatment strategies for antidepressant nonresponse. *J Clin Psychiatry.* 2009 Nov;70(11):e42.
1256. Thase ME. Evaluating atypical antipsychotics in the treatment of refractory depression. *J Clin Psychiatry.* 2009 May;70(5):e14.
1257. Thase ME. Pharmacologic and therapeutic strategies in treatment-resistant depression. Augmentation strategies. *CNS Spectr.* 2009 Mar;14(3 Suppl 4):7-10.

1258. Thase ME, Frank E, Mallinger AG, Hamer T, Kupfer DJ. Treatment of imipramine-resistant recurrent depression, III: Efficacy of monoamine oxidase inhibitors. *J Clin Psychiatry*. 1992 Jan;53(1):5-11.
1259. Thase ME, Friedman ES, Howland RH. Venlafaxine and treatment-resistant depression. *Depress Anxiety*. 2000;12 Suppl 1:55-62.
1260. Thase ME, Friedman ES, Howland RH. Management of treatment-resistant depression: psychotherapeutic perspectives. *J Clin Psychiatry*. 2001;62 Suppl 18:18-24.
1261. Thase ME, Howland RH, Friedman ES. Treating antidepressant nonresponders with augmentation strategies: an overview. *J Clin Psychiatry*. 1998;59 Suppl 5:5-12; discussion 3-5.
1262. Thase ME, Kupfer DJ, Frank E, Jarrett DB. Treatment of imipramine-resistant recurrent depression: II. An open clinical trial of lithium augmentation. *J Clin Psychiatry*. 1989 Nov;50(11):413-7.
1263. Thase ME, Kupfer DJ, Jarrett DB. Treatment of imipramine-resistant recurrent depression: I. An open clinical trial of adjunctive L-triiodothyronine. *J Clin Psychiatry*. 1989 Oct;50(10):385-8.
1264. Thase ME, Rush AJ. When at first you don't succeed: sequential strategies for antidepressant nonresponders. *J Clin Psychiatry*. 1997;58 Suppl 13:23-9.
1265. Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. *Arch Gen Psychiatry*. 2002 Mar;59(3):233-9.
1266. Thase ME, Sachs GS. Bipolar depression: pharmacotherapy and related therapeutic strategies. *Biol Psychiatry*. 2000 Sep 15;48(6):558-72.
1267. Thase ME, Shelton RC, Khan A. Treatment with venlafaxine extended release after SSRI nonresponse or intolerance: a randomized comparison of standard- and higher-dosing strategies. *J Clin Psychopharmacol*. 2006 Jun;26(3):250-8.
1268. Theodorou AE, Katona CL, Davies SL, Hale AS, Kerry SM, Horton RW, et al. 3H-imipramine binding to freshly prepared platelet membranes in depression. *Psychiatry Res*. 1989 Jul;29(1):87-103.
1269. Thienhaus OJ, Margletta S, Bennett JA. A study of the clinical efficacy of maintenance ECT. *J Clin Psychiatry*. 1990 Apr;51(4):141-4.
1270. Thompson C, Thompson CM. Treatment resistant or irresolutely treated? *Int Clin Psychopharmacol*. 1991 Jul;6 Suppl 1:31-8; discussion 8-9.
1271. Tielkes CE, Comijs HC, Verwijk E, Stek ML. The effects of ECT on cognitive functioning in the elderly: a review. *Int J Geriatr Psychiatry*. 2008 Aug;23(8):789-95.
1272. Tierney JG. Treatment-resistant depression: managed care considerations. *J Manag Care Pharm*. 2007 Jul;13(6 Suppl A):S2-7.
1273. Tobin M. Psychopharmacology column: why choose selegiline transdermal system for refractory depression? *Issues Ment Health Nurs*. 2007 Feb;28(2):223-8.
1274. Tremblay P, Blier P. Catecholaminergic strategies for the treatment of major depression. *Curr Drug Targets*. 2006 Feb;7(2):149-58.
1275. Tribo MJ, Andion O, Ros S, Gilaberte M, Gallardo F, Toll A, et al. Clinical characteristics and psychopathological profile of patients with vulvodynia: an observational and descriptive study. *Dermatology*. 2008;216(1):24-30.
1276. Triezenberg D, Vachon D, Helmen J, Schneider D. Clinical inquiries: How should you manage a depressed patient unresponsive to an SSRI? *J Fam Pract*. 2006 Dec;55(12):1081-2, 7.
1277. Triggs WJ, Ricciuti N, Ward HE, Cheng J, Bowers D, Goodman WK, et al. Right and left dorsolateral pre-frontal rTMS treatment of refractory depression: a randomized, sham-controlled trial. *Psychiatry Res*. 2010/07/21 ed 2010:467-74.
1278. Trimble MR. Worldwide use of clomipramine. *J Clin Psychiatry*. 1990 Aug;51 Suppl:51-4; discussion 5-8.

1279. Trivedi MH. Treatment-resistant depression: new therapies on the horizon. *Ann Clin Psychiatry*. 2003 Mar;15(1):59-70.
1280. Trivedi MH, Daly EJ. Treatment strategies to improve and sustain remission in major depressive disorder. *Dialogues Clin Neurosci*. 2008;10(4):377-84.
1281. Trivedi MH, Kleiber BA. Using treatment algorithms for the effective management of treatment-resistant depression. *J Clin Psychiatry*. 2001;62 Suppl 18:25-9.
1282. Trivedi MH, Lin EH, Katon WJ. Consensus recommendations for improving adherence, self-management, and outcomes in patients with depression. *CNS Spectr*. 2007 Aug;12(8 Suppl 13):1-27.
1283. Trivedi MH, Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. *Arch Gen Psychiatry*. 2004 Jul;61(7):669-80.
1284. Trivedi MH, Thase ME, Osuntokun O, Henley DB, Case M, Watson SB, et al. An integrated analysis of olanzapine/fluoxetine combination in clinical trials of treatment-resistant depression. *J Clin Psychiatry*. 2009 Mar;70(3):387-96.
1285. Tsai SJ. Possible involvement of the BDNF-dependent pathway in treatment-emergent suicidality or decreased response to antidepressants. *Med Hypotheses*. 2005;65(5):942-6.
1286. Tsai SJ. Sipatrigine could have therapeutic potential for major depression and bipolar depression through antagonism of the two-pore-domain K⁺ channel TREK-1. *Med Hypotheses*. 2008;70(3):548-50.
1287. Tsourtos G, Spong J, Stough C. The effects of electro-convulsive therapy on the speed of information processing in major depression. *J Affect Disord*. 2007 Nov;103(1-3):263-6.
1288. Tsuchiyama K, Nagayama H, Yamada K, Isogawa K, Katsuragi S, Kiyota A. Predicting efficacy of electroconvulsive therapy in major depressive disorder. *Psychiatry Clin Neurosci*. 2005 Oct;59(5):546-50.
1289. Turkewitz LJ, Casaly JS, Dawson GA, Wirth O. Phenelzine therapy for headache patients with concomitant depression and anxiety. *Headache*. 1992 Apr;32(4):203-7.
1290. Turner TH, Ur E, Grossman A. Naloxone has no effect on hormonal responses to ECT in man. *Psychiatry Res*. 1987 Nov;22(3):207-12.
1291. Turnier-Shea Y, Bruno R, Pridmore S. Daily and spaced treatment with transcranial magnetic stimulation in major depression: a pilot study. *Aust N Z J Psychiatry*. 2006 Sep;40(9):759-63.
1292. Udupa K, Sathyaprabha TN, Thirthalli J, Kishore KR, Raju TR, Gangadhar BN. Modulation of cardiac autonomic functions in patients with major depression treated with repetitive transcranial magnetic stimulation. *J Affect Disord*. 2007 Dec;104(1-3):231-6.
1293. Uhlmann C, Froscher W. Biofeedback treatment in patients with refractory epilepsy: changes in depression and control orientation. *Seizure*. 2001 Jan;10(1):34-8.
1294. Vakili K, Pillay SS, Lafer B, Fava M, Renshaw PF, Bonello-Cintron CM, et al. Hippocampal volume in primary unipolar major depression: a magnetic resonance imaging study. *Biol Psychiatry*. 2000 Jun 15;47(12):1087-90.
1295. van Beusekom BS, van den Broek WW, Birkenhager TK. Long-term follow-up after successful electroconvulsive therapy for depression: a 4- to 8-year naturalistic follow-up study. *J Ect*. 2007 Mar;23(1):17-20.
1296. van den Broek WW, Birkenhager TK, Mulder PG, Bruijn JA, Moleman P. Imipramine is effective in preventing relapse in electroconvulsive therapy-responsive depressed inpatients with prior pharmacotherapy treatment failure: a randomized, placebo-controlled trial. *J Clin Psychiatry*. 2006 Feb;67(2):263-8.
1297. van den Broek WW, de Lely A, Mulder PG, Birkenhager TK, Bruijn JA. Effect of antidepressant medication resistance on short-term response to electroconvulsive therapy. *J Clin Psychopharmacol*. 2004 Aug;24(4):400-3.

1298. van den Broek WW, Groenland TH, Kusuma A, Mulder PG, Bruijn JA. Double-blind placebo controlled study of the effects of etomidate-alfentanil anesthesia in electroconvulsive therapy. *J Ect.* 2004 Jun;20(2):107-11.
1299. Van der Does AJ, Booij L. Cognitive therapy does not prevent a response to tryptophan depletion in patients also treated with antidepressants. *Biol Psychiatry.* 2005 Dec 1;58(11):913-5.
1300. van Hiele LJ. 1-5-Hydroxytryptophan in depression: the first substitution therapy in psychiatry? The treatment of 99 out-patients with 'therapy-resistant' depressions. *Neuropsychobiology.* 1980;6(4):230-40.
1301. Van HL, Dekker J, Peen J, van Aalst G, Schoevers RA. Identifying patients at risk of complete nonresponse in the outpatient treatment of depression. *Psychother Psychosom.* 2008;77(6):358-64.
1302. Van Hunsel F, Wauters A, Vandoolaeghe E, Neels H, Demedts P, Maes M. Lower total serum protein, albumin, and beta- and gamma-globulin in major and treatment-resistant depression: effects of antidepressant treatments. *Psychiatry Res.* 1996 Dec 20;65(3):159-69.
1303. van Praag HM. Serotonin precursors in the treatment of depression. *Adv Biochem Psychopharmacol.* 1982;34:259-86.
1304. Vanderhasselt MA, De Raedt R, Baeken C, Leyman L, D'Haenen H. A single session of rTMS over the left dorsolateral prefrontal cortex influences attentional control in depressed patients. *World J Biol Psychiatry.* 2009;10(1):34-42.
1305. Vanderhasselt MA, De Raedt R, Leyman L, Baeken C. Acute effects of repetitive transcranial magnetic stimulation on attentional control are related to antidepressant outcomes. *J Psychiatry Neurosci.* 2009 Mar;34(2):119-26.
1306. Vanelle JM, Loo H, Galinowski A, de Carvalho W, Bourdel MC, Brochier P, et al. Maintenance ECT in intractable manic-depressive disorders. *Convuls Ther.* 1994 Sep;10(3):195-205.
1307. Vasudev K, Macritchie K, Geddes J, Watson S, Young A. Topiramate for acute affective episodes in bipolar disorder. *Cochrane Database Syst Rev.* 2006(1):CD003384.
1308. Vlissides DN, Jenner FA. The response of endogenously and reactivity depressed patients to electroconvulsive therapy. *Br J Psychiatry.* 1982 Sep;141:239-42.
1309. Volz HP, Faltus F, Magyar I, Moller HJ. Brofaromine in treatment-resistant depressed patients--a comparative trial versus tranylcypromine. *J Affect Disord.* 1994 Mar;30(3):209-17.
1310. Vonck K, Dedeurwaerdere S, De Groote L, Thadani V, Claeys P, Gossiaux F, et al. Generator replacement in epilepsy patients treated with vagus nerve stimulation. *Seizure.* 2005 Mar;14(2):89-99.
1311. Vothknecht S, Kho KH, van Schaick HW, Zwinderman AH, Middelkoop H, Blansjaar BA. Effects of maintenance electroconvulsive therapy on cognitive functions. *J Ect.* 2003 Sep;19(3):151-7.
1312. Wager SG, Klein DF. Drug therapy strategies for treatment-resistant depression. *Psychopharmacol Bull.* 1988;24(1):69-74.
1313. Wagner A, Aberg-Wistedt A, Asberg M, Bertilsson L, Martensson B, Montero D. Effects of antidepressant treatments on platelet tritiated imipramine binding in major depressive disorder. *Arch Gen Psychiatry.* 1987 Oct;44(10):870-7.
1314. Wagner J, Allen NA, Swalley LM, Melkus GD, Whittemore R. Depression, depression treatment, and insulin sensitivity in adults at risk for type 2 diabetes. *Diabetes Res Clin Pract.* 2009 Nov;86(2):96-103.
1315. Wajima Z, Yoshikawa T, Ogura A, Shiga T, Inoue T, Ogawa R. The effects of intravenous lignocaine on haemodynamics and seizure duration during electroconvulsive therapy. *Anaesth Intensive Care.* 2002 Dec;30(6):742-6.
1316. Walderhaug E, Kasserman S, Aikins D, Vojvoda D, Nishimura C, Neumeister A. Effects of duloxetine in treatment-refractory men with posttraumatic stress disorder. *Pharmacopsychiatry.* 2010 Mar;43(2):45-9.

1317. Walpoth M, Hoertnagl C, Mangweth-Matzek B, Kemmler G, Hinterholz J, Conca A, et al. Repetitive transcranial magnetic stimulation in bulimia nervosa: preliminary results of a single-centre, randomised, double-blind, sham-controlled trial in female outpatients. *Psychother Psychosom*. 2008;77(1):57-60.
1318. Walter G, Martin J, Kirkby K, Pridmore S. Transcranial magnetic stimulation: experience, knowledge and attitudes of recipients. *Aust N Z J Psychiatry*. 2001 Feb;35(1):58-61.
1319. Wan DD, Kundhur D, Solomons K, Yatham LN, Lam RW. Mirtazapine for treatment-resistant depression: a preliminary report. *J Psychiatry Neurosci*. 2003 Jan;28(1):55-9.
1320. Wang Y, Fang YR, Chen XS, Chen J, Wu ZG, Yuan CM, et al. A follow-up study on features of sensory gating P50 in treatment-resistant depression patients. *Chin Med J (Engl)*. 2009 Dec;122(24):2956-60.
1321. Warneke L. Managing resistant depression. When patients do not respond to therapy. *Can Fam Physician*. 1993 Apr;39:843-50.
1322. Warneke L. Management of resistant depression. *Can Fam Physician*. 1996 Oct;42:1973-80.
1323. Warren EW, Groome DH. Memory test performance under three different waveforms of ECT for depression. *Br J Psychiatry*. 1984 Apr;144:370-5.
1324. Watkins E, Scott J, Wingrove J, Rimes K, Bathurst N, Steiner H, et al. Rumination-focused cognitive behaviour therapy for residual depression: a case series. *Behav Res Ther*. 2007 Sep;45(9):2144-54.
1325. Weber-Hamann B, Gilles M, Lederbogen F, Heuser I, Deuschle M. Improved insulin sensitivity in 80 nondiabetic patients with MDD after clinical remission in a double-blind, randomized trial of amitriptyline and paroxetine. *J Clin Psychiatry*. 2006 Dec;67(12):1856-61.
1326. Weintraub D. Nortriptyline in geriatric depression resistant to serotonin reuptake inhibitors: case series. *J Geriatr Psychiatry Neurol*. 2001 Spring;14(1):28-32.
1327. Weisler RH. How do you choose a second-line treatment option for depression? *J Clin Psychiatry*. 2010;71 Suppl 1:21-6.
1328. Wells DG, Davies GG, Rosewarne F. Attenuation of electroconvulsive therapy induced hypertension with sublingual nifedipine. *Anaesth Intensive Care*. 1989 Feb;17(1):31-3.
1329. Wells-Parker E, Dill P, Williams M, Stoduto G. Are depressed drinking/driving offenders more receptive to brief intervention? *Addict Behav*. 2006 Feb;31(2):339-50.
1330. Wesner RB, Winokur G. An archival study of depression before and after age 55. *J Geriatr Psychiatry Neurol*. 1988 Oct-Dec;1(4):220-5.
1331. Wesner RB, Winokur G. The influence of age on the natural history of unipolar depression when treated with electroconvulsive therapy. *Eur Arch Psychiatry Neurol Sci*. 1989;238(3):149-54.
1332. Wesson ML, Wilkinson AM, Anderson DN, Cracken CM. Does age predict the long-term outcome of depression treated with ECT? (a prospective study of the long-term outcome of ECT-treated depression with respect to age). *Int J Geriatr Psychiatry*. 1997 Jan;12(1):45-51.
1333. West ED. Electric convulsion therapy in depression: a double-blind controlled trial. *Br Med J (Clin Res Ed)* 1981:355-7.
1334. White K, Simpson G. Combined MAOI-tricyclic antidepressant treatment: a reevaluation. *J Clin Psychopharmacol*. 1981 Sep;1(5):264-82.
1335. White K, Wykoff W, Tynes LL, Schneider L, Zemansky M. Fluvoxamine in the treatment of tricyclic-resistant depression. *Psychiatr J Univ Ott*. 1990 Sep;15(3):156-8.
1336. White PF, Rawal S, Recart A, Thornton L, Litle M, Stool L. Can the bispectral index be used to predict seizure time and awakening after electroconvulsive therapy? *Anesth Analg*. 2003 Jun;96(6):1636-9, table of contents.
1337. Whittal ML, Woody SR, McLean PD, Rachman SJ, Robichaud M. Treatment of obsessions: a randomized controlled trial. *Behav Res Ther*. 2010 Apr;48(4):295-303.
1338. Whyte EM, Basinski J, Farhi P, Dew MA, Begley A, Mulsant BH, et al. Geriatric depression treatment in nonresponders to selective serotonin reuptake inhibitors. *J Clin Psychiatry*. 2004 Dec;65(12):1634-41.

1339. Widepalm K. Comparison of fronto-frontal and temporo-parietal unilateral non-dominant ECT. A retrograde memory study. *Acta Psychiatr Scand.* 1987 Apr;75(4):441-4.
1340. Wijeratne C, Sachdev P. Treatment-resistant depression: critique of current approaches. *Aust N Z J Psychiatry.* 2008 Sep;42(9):751-62.
1341. Wijkstra J, Nolen WA, Algra A, van Vliet IM, Kahn RS. Relapse prevention in major depressive disorder after successful ECT: a literature review and a naturalistic case series. *Acta Psychiatr Scand.* 2000 Dec;102(6):454-60.
1342. Wilhelm K, Mitchell P, Boyce P, Hickie I, Brodaty H, Austin MP, et al. Treatment resistant depression in an Australian context. I: The utility of the term and approaches to management. *Aust N Z J Psychiatry.* 1994 Mar;28(1):14-22.
1343. Wilhelm K, Mitchell P, Sengoz A, Hickie I, Brodaty H, Boyce P. Treatment resistant depression in an Australian context. II: Outcome of a series of patients. *Aust N Z J Psychiatry.* 1994 Mar;28(1):23-33.
1344. Wilkinson AM, Anderson DN, Abou-Saleh MT, Wesson M, Blair JA, Farrar G, et al. 5-Methyltetrahydrofolate level in the serum of depressed subjects and its relationship to the outcome of ECT. *J Affect Disord.* 1994 Nov;32(3):163-8.
1345. Wilkinson P, Hawton K, Andrew B, Fagg J. Does the duration of illness before treatment affect the time taken to recover on treatment in severely depressed women? *J Affect Disord.* 1996 Nov 25;41(2):89-92.
1346. Williams GO. Management of depression in the elderly. *Prim Care.* 1989 Jun;16(2):451-74.
1347. Williams JH, O'Brien JT, Cullum S. Time course of response to electroconvulsive therapy in elderly depressed subjects. *Int J Geriatr Psychiatry.* 1997 May;12(5):563-6.
1348. Williams MD, Rummans T, Sampson S, Knapp R, Mueller M, Husain MM, et al. Outcome of electroconvulsive therapy by race in the Consortium for Research on Electroconvulsive Therapy multisite study. *J Ect.* 2008 Jun;24(2):117-21.
1349. Winokur G, Coryell W, Keller M, Scheftner WA. Relationship of electroconvulsive therapy to course in affective illness: a collaborative study. *Eur Arch Psychiatry Clin Neurosci.* 1990;240(1):54-9.
1350. Woggon B. Methodology of measuring the efficacy of antidepressants--European viewpoint. *Psychopharmacology (Berl).* 1992;106 Suppl:S90-2.
1351. Wolkowitz OM, Reus VI, Roberts E, Manfredi F, Chan T, Raum WJ, et al. Dehydroepiandrosterone (DHEA) treatment of depression. *Biol Psychiatry.* 1997 Feb 1;41(3):311-8.
1352. Yatham LN, Zis AP, Lam RW, Srisurapanont M, McGarvey K, Agbayewa O. Role of serotonin3 receptors in prolactin release induced by electroconvulsive therapy: a study with ondansetron. *Psychiatry Res.* 1996 Feb 28;60(1):33-9.
1353. Yildiz A, Mantar A, Simsek S, Onur E, Gokmen N, Fidaner H. Combination of pharmacotherapy with electroconvulsive therapy in prevention of depressive relapse: a pilot controlled trial. *J ECT.* 2010 Jun;26(2):104-10.
1354. Yip AG, Carpenter LL. Transcranial magnetic stimulation for medication-resistant depression. *J Clin Psychiatry.* 2010 Apr;71(4):502-3.
1355. Yoshimura R, Hori H, Ikenouchi-Sugita A, Umene-Nakano W, Ueda N, Nakamura J. Higher plasma interleukin-6 (IL-6) level is associated with SSRI- or SNRI-refractory depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2009 Jun 15;33(4):722-6.
1356. Yoshimura R, Ikenouchi-Sugita A, Hori H, Umene-Nakano W, Katsuki A, Hayashi K, et al. Adding a low dose atypical antipsychotic drug to an antidepressant induced a rapid increase of plasma brain-derived neurotrophic factor levels in patients with treatment-resistant depression. *Prog Neuropsychopharmacol Biol Psychiatry.* 2010 Mar 17;34(2):308-12.

1357. Yoshimura R, Umene-Nakano W, Ueda N, Ikenouchi-Sugita A, Hori H, Nakamura J. Addition of risperidone to sertraline improves sertraline-resistant refractory depression without influencing plasma concentrations of sertraline and desmethylsertraline. *Hum Psychopharmacol*. 2008 Dec;23(8):707-13.
1358. Young SN. Use of tryptophan in combination with other antidepressant treatments: a review. *J Psychiatry Neurosci*. 1991 Dec;16(5):241-6.
1359. Yu ZJ, Weller RA, Sandidge K, Weller EB. Vagus nerve stimulation: can it be used in adolescents or children with treatment-resistant depression? *Curr Psychiatry Rep*. 2008 Apr;10(2):116-22.
1360. Yukimasa T, Yoshimura R, Tamagawa A, Uozumi T, Shinkai K, Ueda N, et al. High-frequency repetitive transcranial magnetic stimulation improves refractory depression by influencing catecholamine and brain-derived neurotrophic factors. *Pharmacopsychiatry*. 2006 Mar;39(2):52-9.
1361. Yuuki N, Ida I, Oshima A, Kumano H, Takahashi K, Fukuda M, et al. HPA axis normalization, estimated by DEX/CRH test, but less alteration on cerebral glucose metabolism in depressed patients receiving ECT after medication treatment failures. *Acta Psychiatr Scand*. 2005 Oct;112(4):257-65.
1362. Zajecka JM, Jeffries H, Fawcett J. The efficacy of fluoxetine combined with a heterocyclic antidepressant in treatment-resistant depression: a retrospective analysis. *J Clin Psychiatry*. 1995 Aug;56(8):338-43.
1363. Zanardi R, Magri L, Rossini D, Malaguti A, Giordani S, Lorenzi C, et al. Role of serotonergic gene polymorphisms on response to transcranial magnetic stimulation in depression. *Eur Neuropsychopharmacol*. 2007 Oct;17(10):651-7.
1364. Zanardini R, Gazzoli A, Ventriglia M, Perez J, Bignotti S, Rossini PM, et al. Effect of repetitive transcranial magnetic stimulation on serum brain derived neurotrophic factor in drug resistant depressed patients. *J Affect Disord*. 2006 Mar;91(1):83-6.
1365. Zapletal M, Zbytovsky J, Kudrnova K. Clinical experience with maprotilin and maprotilin/clomipramine infusions in resistant depression. *Act Nerv Super (Praha)*. 1982 May;24(2):73-6.
1366. Zeman M, Jirak R, Jachymova M, Vecka M, Tvrzicka E, Zak A. Leptin, adiponectin, leptin to adiponectin ratio and insulin resistance in depressive women. *Neuro Endocrinol Lett*. 2009;30(3):387-95.
1367. Zervas IM, Pehlivanidis AA, Papakostas YG, Markianos M, Papadimitriou GN, Stefanis CN. Effects of TRH administration on orientation time and recall after ECT. *J Ect*. 1998 Dec;14(4):236-40.
1368. Zetin M, Hoepner CT, Bjornson L. Rational antidepressant selection: applying evidence-based medicine to complex real-world patients. *Psychopharmacol Bull*. 2006;39(1):38-104.
1369. Zhang X, Liu K, Sun J, Zheng Z. Safety and feasibility of repetitive transcranial magnetic stimulation (rTMS) as a treatment for major depression during pregnancy. *Arch Womens Ment Health*. 2010 Aug;13(4):369-70.
1370. Zielinski RJ, Roose SP, Devanand DP, Woodring S, Sackeim HA. Cardiovascular complications of ECT in depressed patients with cardiac disease. *Am J Psychiatry*. 1993 Jun;150(6):904-9.
1371. Zimmer B, Rosen J, Thornton JE, Perel JM, Reynolds CF, 3rd. Adjunctive lithium carbonate in nortriptyline-resistant elderly depressed patients. *J Clin Psychopharmacol*. 1991 Aug;11(4):254-6.
1372. Zimmerman M, Coryell W, Pfohl B, Corenthal C, Stangl D. ECT response in depressed patients with and without a DSM-III personality disorder. *Am J Psychiatry*. 1986 Aug;143(8):1030-2.
1373. Zimmerman M, Pfohl B, Coryell W, Stangl D. The prognostic validity of DSM-III axis IV in depressed inpatients. *Am J Psychiatry*. 1987 Jan;144(1):102-6.
1374. Zis AP, Yatham LN, Lam RW, Clark CM, Srisurapanont M, McGarvey K. Effect of stimulus intensity on prolactin and cortisol release induced by unilateral electroconvulsive therapy. *Neuropsychopharmacology*. 1996 Sep;15(3):263-70.

1375. Zisook S, Rush AJ, Haight BR, Clines DC, Rockett CB. Use of bupropion in combination with serotonin reuptake inhibitors. *Biol Psychiatry*. 2006 Feb 1;59(3):203-10.
1376. Zitman FG, Linssen AC, Edelbroek PM, Stijnen T. Low dose amitriptyline in chronic pain: the gain is modest. *Pain*. 1990 Jul;42(1):35-42.
1377. Zobel A, Joe A, Freymann N, Clusmann H, Schramm J, Reinhardt M, et al. Changes in regional cerebral blood flow by therapeutic vagus nerve stimulation in depression: an exploratory approach. *Psychiatry Res*. 2005 Aug 30;139(3):165-79.
1378. Zoger S, Svedlund J, Holgers KM. The effects of sertraline on severe tinnitus suffering--a randomized, double-blind, placebo-controlled study. *J Clin Psychopharmacol*. 2006 Feb;26(1):32-9.
1379. Zohar J, Insel TR. Drug treatment of obsessive-compulsive disorder. *J Affect Disord*. 1987 Sep-Oct;13(2):193-202.
1380. Zornberg GL, Pope HG, Jr. Treatment of depression in bipolar disorder: new directions for research. *J Clin Psychopharmacol*. 1993 Dec;13(6):397-408.
1381. Zorumski CF, Rutherford JL, Burke WJ, Reich T. ECT in primary and secondary depression. *J Clin Psychiatry*. 1986 Jun;47(6):298-300.
1382. Zubenko GS, Mulsant BH, Rifai AH, Sweet RA, Pasternak RE, Marino LJ, Jr., et al. Impact of acute psychiatric inpatient treatment on major depression in late life and prediction of response. *Am J Psychiatry*. 1994 Jul;151(7):987-94.
1383. Zullino D, Baumann P. Lithium augmentation in depressive patients not responding to selective serotonin reuptake inhibitors. *Pharmacopsychiatry*. 2001 Jul;34(4):119-27.
1384. Zusky PM, Biederman J, Rosenbaum JF, Manschreck TC, Gross CC, Weilberg JB, et al. Adjunct low dose lithium carbonate in treatment-resistant depression: a placebo-controlled study. *J Clin Psychopharmacol*. 1988 Apr;8(2):120-4.

Handsearch Results = 310 articles (excluding duplicates)

1. Aarre TF, Dahl AA, Johansen JB, Kjonniksen I, Neckelmann D. Efficacy of repetitive transcranial magnetic stimulation in depression: a review of the evidence. *Nord J Psychiatry*. 2003;57(3):227-32.
2. Abrams R, DeVito RA. Clinical efficacy of unilateral ECT. *Diseases of the nervous system*. 1969;30(4):262-3.
3. American Psychiatric Association. Committee on Electroconvulsive T, Weiner RD. The practice of electroconvulsive therapy : a task force report of the american Psychiatric Association. Washington, D.C.: American Psychiatric Association.
4. Anttila S, Huuhka K, Huuhka M, Illi A, Rontu R, Leinonen E, et al. Catechol-O-methyltransferase (COMT) polymorphisms predict treatment response in electroconvulsive therapy. *Pharmacogenomics J*. 2008 Apr;8(2):113-6.
5. Artigas F, Perez V, Alvarez E. Pindolol induces a rapid improvement of depressed patients treated with serotonin reuptake inhibitors. *Arch Gen Psychiatry*. 1994 Mar;51(3):248-51.
6. Avery D. Transcranial magnetic stimulation in the treatment of depression. *Essent Psychopharmacol*. 2001;4:37-48.
7. Avery D, Winokur G. Mortality in depressed patients treated with electroconvulsive therapy and antidepressants. *Archives of General Psychiatry*. 1976;33(9):1029-37.
8. Azuma H, Fujita A, Otsuki K, Nakano Y, Kamao T, Nakamura C, et al. Ictal electroencephalographic correlates of posttreatment neuropsychological changes in electroconvulsive therapy: a hypothesis-generation study. *J Ect*. 2007 Sep;23(3):163-8.
9. Bagadia VN, Shah LP, Pradhan PV. Evaluation of cognitive effects of ECT (preliminary observations). *Indian J Psychiatry*. 1981;23(4):324-9.

10. Bagby RM, Quilty LC, Segal ZV, McBride CC, Kennedy SH, Costa PT. Personality and differential treatment response in major depression: a randomized controlled trial comparing cognitive-behavioural therapy and pharmacotherapy. *Can J Psychiatry*. 2008 Jun;53(6):361-70.
11. Baghai TC, Marcuse A, Moller HJ, Rupprecht R. [Electroconvulsive therapy at the Department of Psychiatry and Psychotherapy, University of Munich. Development during the years 1995-2002]. *Nervenarzt*. 2005 May;76(5):597-612.
12. Bajbouj M, Lang UE, Neu P, Heuser I. Therapeutic brain stimulation and cortical excitability in depressed patients. *Am J Psychiatry*. 2005 Nov;162(11):2192-3.
13. Baldomero EB, Ubago JG, Cercos CL, Ruiloba JV, Calvo CG, Lopez RP. Venlafaxine extended release versus conventional antidepressants in the remission of depressive disorders after previous antidepressant failure: ARGOS study. *Depress Anxiety*. 2005 Aug 10;22(2):68-76.
14. Barbee JG, Jamhour NJ. Lamotrigine as an augmentation agent in treatment-resistant depression. *Journal of Clinical Psychiatry*. 2002;63(8):737-41.
15. Barker AT, Jalinous R, Freeston H, Jarratt JA. Motor responses to noninvasive brain stimulation in clinical practice. *Electroencephalogr Clin Neurophysiol*. 1985;61:570-4.
16. Barker AT, Jalinous R, Freeston IL. Non-invasive magnetic stimulation of human motor cortex. *Lancet*. 1985;1(8437):1106-7.
17. Barton JL, Mehta S, Snaith RP. The prophylactic value of extra ECT in depressive illness. *Acta Psychiatrica Scandinavica*. 1973;49(4):386-92.
18. Bauer M, Hellweg R, Graf KJ, Baumgartner A. Treatment of refractory depression with high-dose thyroxine. *Neuropsychopharmacology*. 1998 Jun;18(6):444-55.
19. Baxter Jr LR, Schwartz JM, Phelps ME, Mazziotta JC, Guze BH, Selin CE, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Archives of General Psychiatry*. 1989;46(3):243-50.
20. Beale MD, Kellner CH, Pritchett JT, Bernstein HJ, Burns CM, Knapp R. Stimulus dose-titration in ECT: A 2-year clinical experience. *Convulsive Therapy*. 1994;10(2):171-6.
21. Bech P. Meta-analysis of placebo-controlled trials with mirtazapine using the core items of the Hamilton Depression Scale as evidence of a pure antidepressive effect in the short-term treatment of major depression. *International Journal of Neuropsychopharmacology*. 2001;4(4):337-45.
22. Belmaker RH, Fleischmann A. Transcranial magnetic stimulation: a potential new frontier in psychiatry. *Biological Psychiatry*. 1995;38(7):419-21.
23. Ben-Menachem E. Vagus nerve stimulation, side effects, and long-term safety. *Journal of Clinical Neurophysiology*. 2001;18(5):415-8.
24. Ben-Shachar D, Belmaker RH, Grisar N, Klein E. Transcranial magnetic stimulation induces alterations in brain monoamines. *Journal of Neural Transmission*. 1997;104(2-3):191-7.
25. Bergstrom RF, Peyton AL, Lemberger L. Quantification and mechanism of the fluoxetine and tricyclic antidepressant interaction. *Clin Pharmacol Ther*. 1992 Mar;51(3):239-48.
26. Berman RM, Marcus RN, Swanink R, et al. The efficacy and safety of aripiprazole as adjunctive therapy in major depressive disorder : A multicenter, randomized, double-blind, placebo-controlled study. Memphis, TN, ETATS-UNIS: Physicians Postgraduate Press 2007:11.
27. Berman RM, Darnell AM, Miller HL, Anand A, Charney DS. Effect of pindolol in hastening response to fluoxetine in the treatment of major depression: a double-blind, placebo-controlled trial. *Am J Psychiatry*. 1997 Jan;154(1):37-43.
28. Berman RM, Fava M, Thase ME, Trivedi MH, Swanink R, McQuade RD, et al. Aripiprazole augmentation in major depressive disorder: a double-blind, placebo-controlled study in patients with inadequate response to antidepressants. *CNS Spectr*. 2009/05/02 ed 2009:197-206.

29. Bidder TG, Strain JJ, Brunschwig L. Bilateral and unilateral ECT: follow-up study and critique. *American Journal of Psychiatry*. 1970;127(6):737-45.
30. Black DW, Winokur G, Mohandoss E, Woolson RF, Nasrallah A. Does treatment influence mortality in depressives? A follow-up of 1076 patients with major affective disorders. *Annals of Clinical Psychiatry*. 1989;1(3):165-73.
31. Blackburn IM, Moore RG. Controlled acute and follow-up trial of cognitive therapy and pharmacotherapy in out-patients with recurrent depression. *Br J Psychiatry*. 1997 Oct;171:328-34.
32. Bonne O, Krausz Y, Shapira B, Bocher M, Karger H, Gorfine M, et al. Increased cerebral blood flow in depressed patients responding to electroconvulsive therapy. *Journal of Nuclear Medicine*. 1996;37(7):1075-80.
33. Borojjerdi B, Prager A, Muellbacher W, Cohen LG. Reduction of human visual cortex excitability using 1-Hz transcranial magnetic stimulation. *Neurology*. 2000;54(7):1529-31.
34. Bouwer C, Stein DJ. Buspirone is an effective augmenting agent of serotonin selective re-uptake inhibitors in severe treatment-refractory depression. *S Afr Med J*. 1997 Apr;87(4 Suppl):534-7, 40.
35. Bratfos O, Haug JO. Electroconvulsive therapy and antidepressant drugs in manic-depressive disease. Treatment results at discharge and 3 months later. *Acta Psychiatrica Scandinavica*. 1965;41(4):588-96.
36. Brown WA, Harrison W. Are patients who are intolerant to one serotonin selective reuptake inhibitor intolerant to another? *J Clin Psychiatry*. 1995 Jan;56(1):30-4.
37. Browne M, Lapierre YD, Hrdina PD, Horn E. Lithium as an adjunct in the treatment of major depression. *Int Clin Psychopharmacol*. 1990 Apr;5(2):103-10.
38. Bruce EM, Crone N, Fitzpatrick G, Frewin SJ, Gillis A, Lascelles CF, et al. A comparative trial of ECT and tofranil. *American Journal of Psychiatry*. 1960;117:76.
39. Burrows GD, Norman TR, Judd FK. Definition and differential diagnosis of treatment-resistant depression. *International Clinical Psychopharmacology*. 1994;9(SUPPL. 2):5-10.
40. Burt T, Lisanby SH, Sackeim HA. Neuropsychiatric applications of transcranial magnetic stimulation: A meta-analysis. *International Journal of Neuropsychopharmacology*. 2002;5(1):73-103.
41. Calabrese JR, Londeborg PD, Shelton MD, Thase ME. Citalopram treatment of fluoxetine-intolerant depressed patients. *J Clin Psychiatry*. 2003 May;64(5):562-7.
42. Caliyurt O, Vardar E, Tuglu C, Abay E. Effects of propofol on electroconvulsive therapy seizure duration. *Can J Psychiatry*. 2004 Oct;49(10):707-8.
43. Calloway SP, Dolan RJ, Jacoby RJ, Levy R. ECT and cerebral atrophy. A computed tomographic study. *Acta Psychiatrica Scandinavica*. 1981;64(5):442-5.
44. Carney MW, Rogan PA, Sebastian J, Sheffield B. A controlled comparative trial of unilateral and bilateral sinusoidal and pulse E.C.T. in endogenous depression. *Physicians' Drug Manual*. 1976;7:9-128/1.
45. Carpenter LL, Yasmin S, Price LH. A double-blind, placebo-controlled study of antidepressant augmentation with mirtazapine. *Biol Psychiatry*. 2002 Jan 15;51(2):183-8.
46. Cavanagh J, Smyth R, Goodwin GM. Relapse into mania or depression following lithium discontinuation: a 7-year follow-up. *Acta Psychiatr Scand*. 2004 Feb;109(2):91-5.
47. Chae JH, Nahas Z, Lomarev M, Denslow S, Lorberbaum JP, Bohning DE, et al. A review of functional neuroimaging studies of vagus nerve stimulation (VNS). *Journal of Psychiatric Research*. 2003;37(6):443-55.
48. Chen R, Classen J, Gerloff C, Celnik P, Wassermann EM, Hallett M, et al. Depression of motor cortex excitability by low-frequency transcranial magnetic stimulation. *Neurology*. 1997;48(5):1398-403.

49. Chouinard PA, Van Der Werf YD, Leonard G, Paus T. Modulating neural networks with transcranial magnetic stimulation applied over the dorsal premotor and primary motor cortices. *Journal of Neurophysiology*. 2003;90(2):1071-83.
50. Christiansen PE, Behnke K, Black CH, Ohrström JK, Bork-Rasmussen H, Nilsson J. Paroxetine and amitriptyline in the treatment of depression in general practice. *Acta Psychiatrica Scandinavica*. 1996;93(3):158-63.
51. Ciapparelli A, Dell'Osso L, Tundo A, Pini S, Chiavacci MC, Di Sacco I, et al. Electroconvulsive therapy in medication-nonresponsive patients with mixed mania and bipolar depression. *J Clin Psychiatry*. 2001 Jul;62(7):552-5.
52. Clayton AH, Warnock JK, Kornstein SG, Pinkerton R, Sheldon-Keller A, McGarvey EL. A placebo-controlled trial of bupropion SR as an antidote for selective serotonin reuptake inhibitor-induced sexual dysfunction. *J Clin Psychiatry*. 2004 Jan;65(1):62-7.
53. Coffey CE, Lucke J, Weiner RD, Krystal AD, Aque M. Seizure threshold in electroconvulsive therapy (ECT) II. The anticonvulsant effect of ECT. *Biological Psychiatry*. 1995;37(11):777-88.
54. Cole MG, Elie LM, McCusker J, Bellavance F, Mansour A. Feasibility and effectiveness of treatments for post-stroke depression in elderly inpatients: systematic review. *J Geriatr Psychiatry Neurol*. 2001 Spring;14(1):37-41.
55. Cooper-Kazaz R, Lerer B. Efficacy and safety of triiodothyronine supplementation in patients with major depressive disorder treated with specific serotonin reuptake inhibitors. *Int J Neuropsychopharmacol*. 2008 Aug;11(5):685-99.
56. Coppen A, Bailey J. Enhancement of the antidepressant action of fluoxetine by folic acid: a randomised, placebo controlled trial. *J Affect Disord*. 2000 Nov;60(2):121-30.
57. Correll GE, Futter GE. Two case studies of patients with major depressive disorder given low-dose (subanesthetic) ketamine infusions. *Pain Med*. 2006 Jan-Feb;7(1):92-5.
58. Costello CG, Belton GP, Abra JC, Dunn BE. The amnesic and therapeutic effects of bilateral and unilateral ECT. *British Journal of Psychiatry*. 1970;116(530):69-78.
59. Cummings JL. Frontal-subcortical circuits and human behavior. *Archives of Neurology*. 1993;50(8):873-80.
60. Dannon PN, Schreiber S, Dolberg OT, Shemer L, Grunhaus L. Transcranial magnetic stimulation is effective in the treatment of relapse of depression. *International Journal of Psychiatry in Clinical Practice*. 2000;4(3):223-6.
61. Datka W, Siwek M, Dudek D, Maczka G, Zieba A. [Working memory disturbances in patients with major depression after ECT treatment]. *Psychiatr Pol*. 2007 May-Jun;41(3):339-49.
62. Davidson J, McLeod M, Law-Yone B. A comparison of electroconvulsive therapy and combined phenelzine-amitriptyline in refractory depression. *Archives of General Psychiatry*. 1978;35(5):639-42.
63. DeBattista C, Lembke A, Solvason HB, Ghebremichael R, Poirier J. A prospective trial of modafinil as an adjunctive treatment of major depression. *J Clin Psychopharmacol*. 2004 Feb;24(1):87-90.
64. DeBerry S. The effects of meditation-relaxation on anxiety and depression in a geriatric population. *Psychotherapy*. 1982;19(4):512-21.
65. D'Elia G. Comparison of electroconvulsive therapy with unilateral and bilateral stimulation, II: Therapeutic efficacy in endogenous depression. *Acta Psychiatr Scand*. 1970;215:30-43.
66. D'Elia G. Comparison of electroconvulsive therapy with unilateral and bilateral stimulation, III: Anterograde amnesia. *Acta Psychiatr Scand Suppl*. 1970;212:44-60.
67. Demitrack MA, Loo CK, Maixner DF, Avery D, Isenberg K, Dowd SM, et al. Transcranial Magnetic Stimulation (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment. *Society for Biological Psychiatry Annual Meeting and New Research Sessions of the American Psychiatric Association Annual Meeting*.

- Vancouver, B.C. and San Francisco, CA 2009.
68. Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. *Psychopharmacol Bull.* 2009/07/25 ed 2009;5:38.
 69. Demyttenaere K, Jaspers L. Review: Bupropion and SSRI-induced side effects. *J Psychopharmacol.* 2008 Sep;22(7):792-804.
 70. DeRubeis RJ, Feeley M. Determinants of change in cognitive therapy for depression. *Cognitive Therapy and Research.* 1990;14(5):469-82.
 71. DeRubeis RJ, Gelfand LA, Tang TZ, Simons AD. Medications versus cognitive behavior therapy for severely depressed outpatients: Mega-analysis of four randomized comparisons. *American Journal of Psychiatry.* 1999;156(7):1007-13.
 72. Dietzfelbinger T, Möller HJ, Steinmeyer EM. Elektrokrampftherapie als ultima ratio bei antidepressiva-nonrespondern. Therapieresistenz unter Antidepressiva-Behandlung Tropon-Symposium V. 1990:167-85.
 73. Dimitriou EC, Dimitriou CE. Buspirone augmentation of antidepressant therapy. *J Clin Psychopharmacol.* 1998 Dec;18(6):465-9.
 74. Dording CM, Mischoulon D, Petersen TJ, Kornbluh R, Gordon J, Nierenberg AA, et al. The pharmacologic management of SSRI-induced side effects: a survey of psychiatrists. *Ann Clin Psychiatry.* 2002 Sep;14(3):143-7.
 75. Dorr AE, Debonnel G. Effect of vagus nerve stimulation on serotonergic and noradrenergic transmission. *Journal of Pharmacology and Experimental Therapeutics.* 2006;318(2):890-8.
 76. Drevets WC, Videen TO, Price JL, Preskorn SH, Carmichael ST, Raichle ME. A functional anatomical study of unipolar depression. *Journal of Neuroscience.* 1992;12(9):3628-41.
 77. Duffett R, Lelliott P. Auditing electroconvulsive therapy. The third cycle. *British Journal of Psychiatry.* 1998;172(MAY):401-5.
 78. Dunner DL, Russell JM. A long-term, naturalistic study of usual standard-of-care treatment in patients with treatment resistant depression. *Proceedings of the ACNP Annual Meeting, San Juan, Puerto Rico, December 2003.* 2003:150.
 79. Ekers D, Richards D, Gilbody S. A meta-analysis of randomized trials of behavioural treatment of depression. *Psychol Med.* 2008 May;38(5):611-23.
 80. Evans MD, Hollon SD, DeRubeis RJ, Piasecki JM, Grove WM, Garvey MJ, et al. Differential relapse following cognitive therapy and pharmacotherapy for depression. *Archives of General Psychiatry.* 1992;49(10):802-8.
 81. Fabre I, Galinowski A, Oppenheim C, Gallarda T, Meder JF, de Montigny C, et al. Antidepressant efficacy and cognitive effects of repetitive transcranial magnetic stimulation in vascular depression: An open trial. *International Journal of Geriatric Psychiatry.* 2004;19(9):833-42.
 82. Fagiolini A, Kupfer DJ. Is treatment-resistant depression a unique subtype of depression? *Biol Psychiatry.* 2003 Apr 15;53(8):640-8.
 83. Fahy S, Lawlor BA. Discontinuation of lithium augmentation in an elderly cohort. *Int J Geriatr Psychiatry.* 2001 Oct;16(10):1004-9.
 84. Fatemi SH, Emamian ES, Kist DA. Venlafaxine and bupropion combination therapy in a case of treatment-resistant depression. *Ann Pharmacother.* 1999 Jun;33(6):701-3.
 85. Fava GA, Rafanelli C, Silvana G, Canestrari R, Morphy MA. Six-year outcome for cognitive behavioral treatment of residual symptoms in major depression. *American Journal of Psychiatry.* 1998;155(10):1443-5.
 86. Fava M. The combination of buspirone and bupropion in the treatment of depression. *Psychother Psychosom.* 2007;76(5):311-2.
 87. Fava M, Alpert J, Nierenberg AA, Mischoulon D, Otto MW, Zajecka J, et al. A Double-blind, randomized trial of St John's wort, fluoxetine, and placebo in major depressive disorder. *J Clin Psychopharmacol.* 2005 Oct;25(5):441-7.

88. Fava M, McGrath PJ, Sheu WP. Switching to reboxetine: an efficacy and safety study in patients with major depressive disorder unresponsive to fluoxetine. *J Clin Psychopharmacol.* 2003 Aug;23(4):365-9.
89. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry.* 2005 Jan;66(1):85-93.
90. Fawcett J, Kravitz HM, Zajecka JM, Schaff MR. CNS stimulant potentiation of monoamine oxidase inhibitors in treatment-refractory depression. *J Clin Psychopharmacol.* 1991 Apr;11(2):127-32.
91. Feinsod M, Kreinin B, Chistyakov A, Klein E. Preliminary evidence for a beneficial effect of low-frequency, repetitive transcranial magnetic stimulation in patients with major depression and schizophrenia. *Depression and Anxiety.* 1998;7(2):65-8.
92. Fenton L, Fasula M, Ostroff R, Sanacora G. Can cognitive behavioral therapy reduce relapse rates of depression after ECT? a preliminary study. *J Ect.* 2006 Sep;22(3):196-8.
93. Ferreri M, Lavergne F, Berlin I, Payan C, Puech AJ. Benefits from mianserin augmentation of fluoxetine in patients with major depression non-responders to fluoxetine alone. *Acta Psychiatr Scand.* 2001 Jan;103(1):66-72.
94. Fink M. *Convulsive Therapy: Theory and Practice.* New York: Raven 1979.
95. Fink M. Who should get ECT? *The Clinical Science of Electroconvulsive Therapy.* 1993:3-15.
96. Fink M. *Electroshock: restoring the mind.* New York: Oxford University Press 1999.
97. Fink M. Electroconvulsive therapy in medication-resistant depression. *Treatment-Resistant Mood Disorders.* 2001:223-38.
98. Fitzgerald PB, Brown TL, Marston NA, Daskalakis ZJ, de Castella A, Bradshaw JL, et al. Motor cortical excitability and clinical response to rTMS in depression. *J Affect Disord.* 2004 Oct 1;82(1):71-6.
99. Fleminger JJ, de Horne DJ, Nair NP, Nott PN. Differential effect of unilateral and bilateral ECT. *American Journal of Psychiatry.* 1970;127(4):430-6.
100. Floyd M, Scogin F, McKendree-Smith NL, Floyd DL, Rokke PD. Cognitive therapy for depression: a comparison of individual psychotherapy and bibliotherapy for depressed older adults. *Behavior Modification.* 2004;28(2):297-318.
101. Floyd MR. Cognitive therapy for depression: a comparison of individual psychotherapy and bibliotherapy for depressed older adults. *Dissertation Abstracts International.* 1999;58(9 -B):5081.
102. Folkerts H. The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy. *European Archives of Psychiatry and Clinical Neuroscience.* 1996;246(3):155-64.
103. Frank E, Rucci P, Katon W, Barrett J, Williams Jr JW, Oxman T, et al. Correlates of remission in primary care patients treated for minor depression. *General Hospital Psychiatry.* 2002;24(1):12-9.
104. Fredman SJ, Fava M, Kienke AS, White CN, Nierenberg AA, Rosenbaum JF. Partial response, nonresponse, and relapse with selective serotonin reuptake inhibitors in major depression: a survey of current "next-step" practices. *J Clin Psychiatry.* 2000 Jun;61(6):403-8.
105. Freeman CPL, Basson JV, Crighton A. Double-blind controlled trial of electroconvulsive therapy (E.C.T.) and simulated E.C.T. in depressive illness. *Lancet.* 1978;1(8067):738-40.
106. Fromholt P, Christensen AL, Sand Stromgren L. The effects of unilateral and bilateral electroconvulsive therapy on memory. *Acta Psychiatrica Scandinavica.* 1973;49(4):466-78.
107. Gallagher DE, Thompson LW. Treatment of major depressive disorder in older adult outpatients with brief psychotherapies. *Psychotherapy.* 1982;19(4):482-90.
108. Gallagher-Thompson D, Steffen AM. Comparative effects of cognitive-behavioral and brief psychodynamic psychotherapies for depressed family caregivers. *Journal of Consulting and Clinical Psychology.* 1994;62(3):543-9.

109. Geddes J, Carney S, Cowen P, Goodwin G, Rogers R, Dearness K, et al. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet*. 2003 Mar 8;361(9360):799-808.
110. George MS, Belmaker RH. *Transcranial magnetic stimulation in neuropsychiatry*. Washington, DC: American Psychiatric Press 2000.
111. George MS, Wassermann EM. Rapid-rate transcranial magnetic stimulation and ECT. *Convulsive Therapy*. 1994;10(4):251-4; discussion 5.
112. Gitlin MJ, Suri R, Altshuler L, Zuckerbrow-Miller J, Fairbanks L. Bupropion-sustained release as a treatment for SSRI-induced sexual side effects. *J Sex Marital Ther*. 2002 Mar-Apr;28(2):131-8.
113. Gloaguen V, Cottraux J, Cucherat M, Blackburn IM. A meta-analysis of the effects of cognitive therapy in depressed patients. *J Affect Disord*. 1998 Apr;49(1):59-72.
114. Goodwin FK, Prange AJ, Jr., Post RM, Muscettola G, Lipton MA. Potentiation of antidepressant effects by L-triiodothyronine in tricyclic nonresponders. *Am J Psychiatry*. 1982 Jan;139(1):34-8.
115. Gormsen L, Ribe AR, Raun P, Rosenberg R, Videbech P, Vestergaard P, et al. Pain thresholds during and after treatment of severe depression with electroconvulsive therapy. *Eur J Pain*. 2004 Oct;8(5):487-93.
116. Greenblatt M, Grosser GH, Wechsler H. Differential response of hospitalized depressed patients to somatic therapy. *Am J Psychiatry*. 1964;120:935-43.
117. Gregory S, Shawcross CR, Gill D. The Nottingham ECT study. A double-blind comparison of bilateral, unilateral and simulated ECT in depressive illness. *British Journal of Psychiatry* 1985:520-4.
118. Grisar N, Yaroslavsky U, Abarbanel J, Lamberg T, Belmaker RH. Transcranial magnetic stimulation in depression and schizophrenia. *European Neuropsychopharmacology*. 1994;4(3):287-8.
119. Gross M, Nakamura L, Pascual-Leone A, Fregni F. Has repetitive transcranial magnetic stimulation (rTMS) treatment for depression improved? A systematic review and meta-analysis comparing the recent vs. the earlier rTMS studies. *Acta Psychiatr Scand*. 2007 Sep;116(3):165-73.
120. Grunhaus L, Dolberg O, Lustig M. Relapse and recurrence following a course of ECT: Reasons for concern and strategies for further investigation. *Journal of Psychiatric Research*. 1995;29(3):165-72.
121. Gupta S, Ghaly N, Dewan M. Augmenting fluoxetine with dextroamphetamine to treat refractory depression. *Hosp Community Psychiatry*. 1992 Mar;43(3):281-3.
122. Guzzetta F, Tondo L, Centorrino F, Baldessarini RJ. Lithium treatment reduces suicide risk in recurrent major depressive disorder. *J Clin Psychiatry*. 2007 Mar;68(3):380-3.
123. Halliday AM, Davison K, Browne MW, Kreeger LC. A comparison of the effects on depression and memory of bilateral E.C.T. and unilateral E.C.T. to the dominant and non-dominant hemispheres. *British Journal of Psychiatry*. 1968;114(513):997-1012.
124. Hannan N, Hamzah Z, Akinpeloye HO, Meagher D. Venlafaxine-mirtazapine combination in the treatment of persistent depressive illness. *J Psychopharmacol*. 2007 Mar;21(2):161-4.
125. Hansen PE, Ravnkilde B, Videbech P, Clemmensen K, Sturlason R, Reiner M, et al. Low-Frequency Repetitive Transcranial Magnetic Stimulation Inferior to Electroconvulsive Therapy in Treating Depression. *J ECT*. 2010/03/31 ed 2010.
126. Hanss R, Bauer M, Bein B, Goeder R, Buttgerit B, Schulz-Du Bois AC, et al. Bispectral index-controlled anaesthesia for electroconvulsive therapy. *Eur J Anaesthesiol*. 2006 Mar;23(3):202-7.
127. Heikman P, Tuunainen A, Sailas E, Kuoppasalmi K. Seizures induced by low-dose right unilateral and bifrontal electroconvulsive stimuli. *J Ect*. 2003 Dec;19(4):189-93.

128. Helmstaedter C, Hoppe C, Elger CE. Memory alterations during acute high-intensity vagus nerve stimulation. *Epilepsy Research*. 2001;47(1-2):37-42.
129. Henry TR, Votaw JR, Pennell PB, Epstein CM, Bakay RAE, Faber TL, et al. Acute blood flow changes and efficacy of vagus nerve stimulation in partial epilepsy. *Neurology*. 1999;52(6):1166-73.
130. Herrington RN, Bruce A, Johnstone EC, Lader MH. Comparative trial of L tryptophan and E.C.T. in severe depressive illness. *Lancet*. 1974;2(7883):731-4.
131. Heshe J, Röder E, Theilgaard A. Unilateral and bilateral ECT. A psychiatric and psychological study of therapeutic effect and side effects. *Acta Psychiatrica Scandinavica, Supplement*. 1978(275):1-180.
132. Hestad KA, Tonseth S, Stoen CD, Ueland T, Aukrust P. Raised plasma levels of tumor necrosis factor alpha in patients with depression: normalization during electroconvulsive therapy. *J Ect* 2003:183-8.
133. Hihn H, Baune BT, Michael N, Markowitsch H, Arolt V, Pfleiderer B. Memory performance in severely depressed patients treated by electroconvulsive therapy. *J Ect*. 2006 Sep;22(3):189-95.
134. Hoflich G, Kasper S, Hufnagel A, Ruhrmann S, Moller HJ. Application of transcranial magnetic stimulation in treatment of drug-resistant major depression - A report of two cases. *Human Psychopharmacology*. 1993;8(5):361-5.
135. Holtzheimer 3rd PE, Russo J, Avery DH. A meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression. *Psychopharmacology bulletin*. 2001;35(4):149-69.
136. Holtzheimer P, Russo J, Avery D. Erratum for "a meta-analysis of repetitive transcranial magnetic stimulation in the treatment of depression". *Psychopharmacol Bull*. 2003;37:5.
137. Holtzheimer PE, Avery D, Schlaepfer TE. Antidepressant effects of repetitive transcranial magnetic stimulation [4]. *British Journal of Psychiatry*. 2004;184(JUNE):541-2.
138. Howland RH. Chronic depression. *Hospital and Community Psychiatry*. 1993;44(7):633-9.
139. Huang CC, Su TP, Shan IK, Chang K, Wei IH. An open trial of daily left prefrontal cortex repetitive transcranial magnetic stimulation for treating medication-resistant depression. *Eur Psychiatry*. 2004 Dec;19(8):523-4.
140. Hutchinson J, Smedberg D. Treatment of depression: A comparative study of ECT and six drugs. *Br J Psychiatry*. 1963;109:536-8.
141. Huuhka K, Anttila S, Huuhka M, Hietala J, Huhtala H, Mononen N, et al. Dopamine 2 receptor C957T and catechol-o-methyltransferase Val158Met polymorphisms are associated with treatment response in electroconvulsive therapy. *Neurosci Lett* 2008:79-83.
142. Huuhka MJ, Seinela L, Reinikainen P, Leinonen EV. Cardiac arrhythmias induced by ECT in elderly psychiatric patients: experience with 48-hour Holter monitoring. *J Ect*. 2003 Mar;19(1):22-5.
143. Iosifescu DV, Bolo NR, Nierenberg AA, Jensen JE, Fava M, Renshaw PF. Brain bioenergetics and response to triiodothyronine augmentation in major depressive disorder. *Biol Psychiatry*. 2008 Jun 15;63(12):1127-34.
144. Jacobsen FM. Possible augmentation of antidepressant response by buspirone. *J Clin Psychiatry*. 1991 May;52(5):217-20.
145. Janicak PG, Nahas Z, Lisanby SH, Solvason HB, Sampson S, McDonald W, et al. Durability of acute response to TMS in the treatment of major depression: relapse during a continuation pharmacotherapy extension study. *Society for Biological Psychiatry Annual Meeting*; 2007 May; San Diego, CA; 2007.
146. Joffe RT, Levitt AJ, Sokolov STH, Young LT. Response to an open trial of a second SSRI in major depression. *Journal of Clinical Psychiatry*. 1996;57(3):114-5.
147. Judd LL, Akiskal HS, Schettler PJ, Coryell W, Endicott J, Maser JD, et al. A prospective investigation of the natural history of the long-term weekly symptomatic status of bipolar II disorder. *Arch Gen Psychiatry* 2003:261-9.

148. Kaplan B, Chistyakov A, Kreinin I, Hafner H, Feinsod M, Klein E. The effect of electroconvulsive therapy and repetitive transcranial magnetic stimulation on cortical excitability in patients with major depression. *Muscle & Nerve Supplement*. 2003;12.
149. Kasper S, Heiden A. Do SSRIs differ in their antidepressant efficacy. *Human Psychopharmacology*. 1995;10(SUPPL. 3).
150. Keller MB, Gelenberg AJ, Hirschfeld RMA, Rush AJ, Thase ME, Kocsis JH, et al. The treatment of chronic depression, Part 2: A double-blind, randomized trial of sertraline and imipramine. *Journal of Clinical Psychiatry*. 1998;59(11):598-607.
151. Keller MB, Lavori PW, Mueller TI, Endicott J, Coryell W, Hirschfeld RMA, et al. Time to recovery, chronicity, and levels of psychopathology in major depression: A 5-year prospective follow-up of 431 subjects. *Archives of General Psychiatry*. 1992;49(10):809-16.
152. Keller MB, Lavori PW, Rice J. The persistent risk of chronicity in recurrent episodes of nonbipolar major depressive disorder: A prospective follow-up. *Am J Psychiatry*. 1992;143(1):24-8.
153. Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *New England Journal of Medicine*. 2000;342(20):1462-70.
154. Kellner CH, Fink M, Knapp R, Petrides G, Husain M, Rummans T, et al. Relief of expressed suicidal intent by ECT: a consortium for research in ECT study. *Am J Psychiatry*. 2005 May;162(5):977-82.
155. Kennedy SH, McCann SM, Masellis M, McIntyre RS, Raskin J, McKay G, et al. Combining bupropion SR with venlafaxine, paroxetine, or fluoxetine: a preliminary report on pharmacokinetic, therapeutic, and sexual dysfunction effects. *J Clin Psychiatry*. 2002 Mar;63(3):181-6.
156. Kho KH, van Vreeswijk MF, Simpson S, Zwinderman AH. A meta-analysis of electroconvulsive therapy efficacy in depression. *J Ect*. 2003 Sep;19(3):139-47.
157. Klausner EJ, Clarkin JF, Spielman L, Pupo C, Abrams R, Alexopoulos GS. Late-life depression and functional disability: the role of goal-focused group psychotherapy. *International Journal of Geriatric Psychiatry*. 1998;13(10):707-16.
158. Kocsis JH, Friedman RA, Markowitz JC, Leon AC, Miller NL, Gniwesch L, et al. Maintenance therapy for chronic depression: A controlled clinical trial of desipramine. *Archives of General Psychiatry*. 1996;53(9):769-76.
159. Koran LM, Gelenberg AJ, Kornstein SG, Howland RH, Friedman RA, DeBattista C, et al. Sertraline versus imipramine to prevent relapse in chronic depression. *Journal of Affective Disorders*. 2001;65(1):27-36.
160. Kozel FA, George MS. Meta-analysis of left prefrontal repetitive transcranial magnetic stimulation (rTMS) to treat depression. *J Psychiatr Pract*. 2002;8(5):270-5.
161. Kraus RP. Rapid cycling triggered by pindolol augmentation of paroxetine, but not with desipramine. *Depression*. 1996;4(2):92-4.
162. Kroessler D. Relative efficacy rates for therapies of delusional depression. *Convulsive Therapy*. 1985;1(3):173-82.
163. Kuhs H. Degrees of treatment resistance in depressive disorders on the basis of somatotherapeutic trials. *STUFEN IN DER BEHANDLUNGSRESISTENZ BEI DEPRESSIVEN STORUNGEN, DEFINIERT NACH SOMATOTHERAPEUTISCHEN VERFAHREN*. 1995;66(7):561-7.
164. Kunugi H, Ida I, Owashi T, Kimura M, Inoue Y, Nakagawa S, et al. Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic-pituitary-adrenal (HPA) axis abnormalities in major depressive episode: a Multicenter Study. *Neuropsychopharmacology* 2006:212-20.
165. Laidlaw K, Davidson K, Toner H, Jackson G, Clark S, Law J, et al. A randomised controlled trial of cognitive behaviour therapy vs treatment as usual in the treatment of mild to moderate late life depression. *Int J Geriatr Psychiatry*. 2008 Aug;23(8):843-50.

166. Lalitanatpong D. The use of electroconvulsive therapy and the length of stay of psychiatric inpatients at King Chulalongkorn Memorial Hospital, Thai Red Cross Society. *J Med Assoc Thai* 2005;S142-8.
167. Lam RW, Chan P, Wilkins-Ho M, Yatham LN. Repetitive Transcranial Magnetic Stimulation for Treatment-Resistant Depression: A Systematic Review and Metaanalysis. *Canadian journal of psychiatry Revue canadienne de psychiatrie*. 2008;53(9):621.
168. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. *JAMA*. 2008/10/02 ed 2008;1551-65.
169. Levitt AJ, Joffe RT, Kamil R, McIntyre R. Do depressed subjects who have failed both fluoxetine and a tricyclic antidepressant respond to the combination? *J Clin Psychiatry*. 1999 Sep;60(9):613-6.
170. Levy R. The clinical evaluation of unilateral electroconvulsive therapy. *British Journal of Psychiatry*. 1968;114(509):459-63.
171. Licht RW, Qvitau S. Treatment strategies in patients with major depression not responding to first-line sertraline treatment. A randomised study of extended duration of treatment, dose increase or mianserin augmentation. *Psychopharmacology (Berl)*. 2002 May;161(2):143-51.
172. Lincoln NB, Flannaghan T. Cognitive behavioral psychotherapy for depression following stroke: A randomized controlled trial. *Stroke*. 2003;34(1):111-5.
173. Linet LS. Treatment of a refractory depression with a combination of fluoxetine and d-amphetamine. *Am J Psychiatry*. 1989 Jun;146(6):803-4.
174. Loo CK, Mitchell PB. A review of the efficacy of transcranial magnetic stimulation (TMS) treatment for depression, and current and future strategies to optimize efficacy. *J Affect Disord*. 2005 Nov;88(3):255-67.
175. Lyketsos CG, DelCampo L, Steinberg M, Miles Q, Steele CD, Munro C, et al. Treating depression in Alzheimer disease: efficacy and safety of sertraline therapy, and the benefits of depression reduction: the DIADS. *Archives of General Psychiatry*. 2003;60(7):737-46.
176. Maihofner C, Ropohl A, Reulbach U, Hiller M, Elstner S, Kornhuber J, et al. Effects of repetitive transcranial magnetic stimulation in depression: a magnetoencephalographic study. *Neuroreport*. 2005 Nov 7;16(16):1839-42.
177. Malitz S, Sackeim H, Decina P. Low dosage ECT: Electrode placement and acute physiological and cognitive effects. *Am J Psychiatry*. 1984;4:47-53.
178. Mandel MR, Welch CA, Mieske M. Prediction of response to ECT in tricyclic-intolerant or tricyclic-resistant depressed patients. *McLean Hosp J*. 1977;4:203-9.
179. Manganotti P, Bortolomasi M, Zanette G, Pawelzik T, Giacomuzzi M, Fiaschi A. Intravenous clomipramine decreases excitability of human motor cortex. A study with paired magnetic stimulation. *Journal of the Neurological Sciences*. 2001;184(1):27-32.
180. Marangell LB, Suppes T, Zboyan HA, Prashad SJ, Fischer G, Snow D, et al. A 1-year pilot study of vagus nerve stimulation in treatment-resistant rapid-cycling bipolar disorder. *J Clin Psychiatry*. 2008 Feb;69(2):183-9.
181. McDonald IM, Perkins M, Marjerrison G, Podilsky M. A controlled comparison of amitriptyline and electroconvulsive therapy in the treatment of depression. *American Journal of Psychiatry*. 1966;122(12):1427-31.
182. Michelson D, Kociban K, Tamura R, Morrison MF. Mirtazapine, yohimbine or olanzapine augmentation therapy for serotonin reuptake-associated female sexual dysfunction: a randomized, placebo controlled trial. *J Psychiatr Res*. 2002 May-Jun;36(3):147-52.
183. Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, et al. The treatment of chronic depression, Part 3: Psychosocial functioning before and after treatment with sertraline or imipramine. *Journal of Clinical Psychiatry*. 1998;59(11):608-19.

184. Moustgaard G. Treatment-refractory depression successfully treated with the combination of mirtazapine and lithium. *J Clin Psychopharmacol* 2000;268.
185. Mulrow CD, Williams JW, Jr., Trivedi M, Chiquette E, Aguilar C, Cornell JE, et al. Treatment of depression--newer pharmacotherapies. *Psychopharmacol Bull*. 1998;34(4):409-795.
186. Nahas Z, Teneback C, Chae JH, Mu Q, Molnar C, Kozel FA, et al. Serial vagus nerve stimulation functional MRI in treatment-resistant depression. *Neuropsychopharmacology*. 2007 Aug;32(8):1649-60.
187. Naritoku DK, Terry WJ, Helfert RH. Regional induction of fos immunoreactivity in the brain by anticonvulsant stimulation of the vagus nerve. *Epilepsy Research*. 1995;22(1):53-62.
188. Nelson AL, Cohen JT, Greenberg D, Kent DM. Much cheaper, almost as good: decrementally cost-effective medical innovation. *Ann Intern Med*. 2009/11/04 ed 2009;662-7.
189. Nemeroff CB, Heim CM, Thase ME, Klein DN, Rush AJ, Schatzberg AF, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci U S A*. 2003/11/15 ed 2003;14293-6.
190. Nemeroff CB, Mayberg HS, Krahl SE, McNamara J, Frazer A, Henry TR, et al. VNS therapy in treatment-resistant depression: Clinical evidence and putative neurobiological mechanisms. *Neuropsychopharmacology*. 2006;31(7):1345-55.
191. Nemets B, Mishory A, Levine J, Belmaker RH. Inositol addition does not improve depression in SSRI treatment failures. *J Neural Transm*. 1999;106(7-8):795-8.
192. Nemets B, Stahl Z, Belmaker RH. Addition of omega-3 fatty acid to maintenance medication treatment for recurrent unipolar depressive disorder. *Am J Psychiatry*. 2002 Mar;159(3):477-9.
193. Nestler EJ. Antidepressant treatments in the 21st century. *Biological Psychiatry*. 1998;44(7):526-33.
194. Nierenberg AA, Amsterdam JD. Treatment-resistant depression: Definition and treatment approaches. *Journal of Clinical Psychiatry*. 1990;51(6 SUPPL.):39-47.
195. Nierenberg AA, Feighner JP, Rudolph R, Cole JO, Sullivan J. Venlafaxine for treatment-resistant unipolar depression. *Journal of Clinical Psychopharmacology*. 1994;14(6):419-23.
196. Nierenberg AA, Papakostas GI, Petersen T, Kelly KE, Iacoviello BM, Worthington JJ, et al. Nortriptyline for treatment-resistant depression. *J Clin Psychiatry*. 2003 Jan;64(1):35-9.
197. Nobuhara K, Okugawa G, Minami T, Takase K, Yoshida T, Yagyu T, et al. Effects of electroconvulsive therapy on frontal white matter in late-life depression: a diffusion tensor imaging study. *Neuropsychobiology* 2004;48-53.
198. Nyhuis PW, Gastpar M, Scherbaum N. Opiate treatment in depression refractory to antidepressants and electroconvulsive therapy. *J Clin Psychopharmacol*. 2008 Oct;28(5):593-5.
199. O'Connor MK, Knapp R, Husain M, Rummans TA, Petrides G, Smith G, et al. The influence of age on the response of major depression to electroconvulsive therapy: a C.O.R.E. Report. *Am J Geriatr Psychiatry*. 2001 Fall;9(4):382-90.
200. Okamoto T, Yoshimura R, Ikenouchi-Sugita A, Hori H, Umene-Nakano W, Inoue Y, et al. Efficacy of electroconvulsive therapy is associated with changing blood levels of homovanillic acid and brain-derived neurotrophic factor (BDNF) in refractory depressed patients: a pilot study. *Prog Neuropsychopharmacol Biol Psychiatry*. 2008 Jul 1;32(5):1185-90.
201. Okazaki M, Tominaga K, Higuchi H, Utagawa I, Nakamura E, Noguchi M, et al. Predictors of response to electroconvulsive therapy obtained using the three-factor structure of the Montgomery and Asberg Depression Rating Scale for treatment-resistant depressed patients. *J Ect*. Jun;26(2):87-90.

202. Oquendo MA, Malone KM, Ellis SP, Sackeim HA, Mann JJ. Inadequacy of antidepressant treatment for patients with major depression who are at risk for suicidal behavior. *American Journal of Psychiatry*. 1999;156(2):190-4.
203. Ozsoy S, Esel E, Kula M. Serum oxytocin levels in patients with depression and the effects of gender and antidepressant treatment. *Psychiatry Res* 2009:249-52.
204. Parker G, Roy K, Hadzi-Pavlovic D, Pedic F. Psychotic (delusional) depression: A meta-analysis of physical treatments. *Journal of Affective Disorders*. 1992;24(1):17-24.
205. Parker V, Nobler MS, Pedley TA, Sackeim HA. A unilateral, prolonged, nonconvulsive seizure in a patient treated with bilateral ECT. *J Ect* 2001:141-5.
206. Pascual-Leone A, Houser CM, Reese K, Shotland LI, Grafman J, Sato S, et al. Safety of rapid-rate transcranial magnetic stimulation in normal volunteers. *Electroencephalography and Clinical Neurophysiology - Electromyography and Motor Control*. 1993;89(2):120-30.
207. Pascual-Leone A, Tormos JM, Keenan J, Tarazona F, Cañete C, Catalá MD. Study and modulation of human cortical excitability with transcranial magnetic stimulation. *Journal of Clinical Neurophysiology*. 1998;15(4):333-43.
208. Paul SM, Extein I, Calil HM. Use of ECT with treatment-resistant depressed patients at the National Institute of Mental Health. *American Journal of Psychiatry*. 1981;138(4):486-9.
209. Paykel ES, Scott J, Cornwall PL, Abbott R, Crane C, Pope M, et al. Duration of relapse prevention after cognitive therapy in residual depression: follow-up of controlled trial. *Psychol Med*. 2005/04/22 ed 2005:59-68.
210. Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, et al. Prevention of relapse in residual depression by cognitive therapy. A controlled trial. *Archives of General Psychiatry*. 1999;56(9):829-35.
211. Perez V, Gilaberte I, Faries D, Alvarez E, Artigas F. Randomised, double-blind, placebo-controlled trial of pindolol in combination with fluoxetine antidepressant treatment. *Lancet*. 1997 May 31;349(9065):1594-7.
212. Peselow ED, Filippi AM, Goodnick P, Barouche F, Fieve RR. The short- and long-term efficacy of paroxetine HCl: B. Data from a double-blind crossover study and from a year-long term trial vs. imipramine and placebo. *Psychopharmacol Bull*. 1989/01/01 ed 1989:272-6.
213. Peselow ED, Filippi AM, Goodnick P, Barouche F, Fieve RR. The short- and long-term efficacy of paroxetine HCl: A. Data from a 6-week double-blind parallel design trial vs. imipramine and placebo. *Psychopharmacol Bull*. 1989;25(2):267-71.
214. Philibert RA, Richards L, Lynch CF, Winokur G. Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. *Journal of Clinical Psychiatry*. 1995;56(7 SUPPL.):390-4.
215. Poirier MF. [The concept of resistant depression and therapeutic strategies, particularly, with venlafaxine]. *Encephale*. 1999 Jun;25 Spec No 2:55-7; discussion 8-61.
216. Pope HG, Jr., McElroy SL, Nixon RA. Possible synergism between fluoxetine and lithium in refractory depression. *Am J Psychiatry*. 1988 Oct;145(10):1292-4.
217. Prudic J, Sackeim HA, Devanand DP. Medication resistance and clinical response to electroconvulsive therapy. *Psychiatry Research*. 1990;31(3):287-96.
218. Ramasubbu R. Treatment of resistant depression by adding noradrenergic agents to lithium augmentation of SSRIs. *Ann Pharmacother*. 2002 Apr;36(4):634-40.
219. Rapaport MH, Gharabawi GM, Canuso CM, Mahmoud RA, Keller MB, Bossie CA, et al. Effects of risperidone augmentation in patients with treatment-resistant depression: Results of open-label treatment followed by double-blind continuation. *Neuropsychopharmacology*. 2006/06/09 ed 2006:2505-13.

220. Rasanen P, Hakko H, Tiihonen J, Mitchell B, Balter Award--1998. Pindolol and major affective disorders: a three-year follow-up study of 30,485 patients. *J Clin Psychopharmacol*. 1999 Aug;19(4):297-302.
221. Rasmussen KG, Karpyak VM, Hammill SC. Lack of effect of ECT on Holter monitor recordings before and after treatment. *J Ect*. 2004 Mar;20(1):45-7.
222. Rasmussen KG, Mueller M, Kellner CH, Knapp RG, Petrides G, Rummans TA, et al. Patterns of psychotropic medication use among patients with severe depression referred for electroconvulsive therapy: data from the Consortium for Research on Electroconvulsive Therapy. *J Ect*. 2006 Jun;22(2):116-23.
223. Rasmussen P, Andersson JE, Koch P, Secher NH, Quistorff B. Glycopyrrolate prevents extreme bradycardia and cerebral deoxygenation during electroconvulsive therapy. *J Ect*. 2007 Sep;23(3):147-52.
224. Rehor G, Conca A, Schlotter W, Vonthein R, Bork S, Bode R, et al. [Relapse rate within 6 months after successful ECT: a naturalistic prospective peer- and self-assessment analysis]. *Neuropsychiatr* 2009:157-63.
225. Reynaert-Dupuis C, Zdanowicz N, Group AG-BS, Leyman S, Mignon A, Seghers S. Efficacy and tolerance of venlafaxine in depressed patients switched from prior antidepressant treatment. *PRIMARY CARE PSYCHIATRY*. 2002;8:63-8.
226. Reynolds, III, C. F., Frank E, Houck PR, Mazumdar S, Dew MA, Cornes C, et al. Which elderly patients with remitted depression remain well with continued interpersonal psychotherapy after discontinuation of antidepressant medication? *American Journal of Psychiatry*. 1997;154(7):958-62.
227. Reynolds, III, C. F., Frank E, Kupfer DJ, Thase ME, Perel JM, Mazumdar S, et al. Treatment outcome in recurrent major depression: A post hoc comparison of elderly ('young old') and midlife patients. *American Journal of Psychiatry*. 1996;153(10):1288-92.
228. Reynolds, III, C. F., Frank E, Perel JM, Mazumdar S, Dew MA, Begley A, et al. High relapse rate after discontinuation of adjunctive medication for elderly patients with recurrent major depression. *American Journal of Psychiatry*. 1996;153(11):1418-22.
229. Reynolds, III, C. F., Miller MD, Pasternak RE, Frank E, Perel JM, Cornes C, et al. Treatment of bereavement-related major depressive episodes in later life: A controlled study of acute and continuation treatment with nortriptyline and interpersonal psychotherapy. *American Journal of Psychiatry*. 1999;156(2):202-8.
230. Reynolds I, C. F., Frank E, Perel JM, Imber SD, Cornes C, Miller MD, et al. Nortriptyline and interpersonal psychotherapy as maintenance therapies for recurrent major depression. A randomized controlled trial in patients older than 59 years. *Journal of the American Medical Association*. 1999;281(1):39-45.
231. Reynolds I, C. F., Frank E, Perel JM, Miller MD, Cornes C, Rifai AH, et al. Treatment of consecutive episodes of major depression in the elderly. *American Journal of Psychiatry*. 1994;151(12):1740-3.
232. Rich CL, Spiker DG, Jewell SW. The efficiency of ECT: I. Response rate in depressive episodes. *Psychiatry Research*. 1984;11(3):167-76.
233. Robin A, Harris JA. A controlled comparison of imipramine and electroplexy. *J Ment Sci*. 1962;108:217-9.
234. Rocha FL, Hara C. Lamotrigine augmentation in unipolar depression. *Int Clin Psychopharmacol*. 2003 Mar;18(2):97-9.
235. Roose SP. Methodological issues in the diagnosis, treatment, and study of refractory depression. *Treatment Strategies for Refractory Depression*. 1990:1-9.
236. Rosa MA, Rosa MO, Daltio CS, Abreu LN, Marcolin MA. Open trial on the efficacy of right unilateral electroconvulsive therapy with titration and high charge. *J Ect*. 2006 Dec;22(4):237-9.
237. Ross J. Discontinuation of lithium augmentation in geriatric patients with unipolar depression: a systematic review. *Can J Psychiatry*. 2008 Feb;53(2):117-20.

238. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol.* 2009 Dec;120(12):2008-39.
239. Rothschild AJ, Williamson DJ, Tohen MF, Schatzberg A, Andersen SW, Van Campen LE, et al. A double-blind, randomized study of olanzapine and olanzapine/fluoxetine combination for major depression with psychotic features. *J Clin Psychopharmacol.* 2004 Aug;24(4):365-73.
240. Ruhwinkel B, Tolle R. [Modified insulin treatment of therapy refractory depression]. *Psychiatr Prax.* 1995 Mar;22(2):64-7.
241. Rush AJ, George MS, Sackeim HA, Marangell LB, Husain MM, Giller C, et al. Vagus nerve stimulation (VNS) for treatment-resistant depressions: a multicenter study. *Biological Psychiatry.* 2000;47(4):276-86.
242. Rush AJ, Gullion CM, Roffwarg HP. When do patients respond to tricyclic antidepressants? *Biol Psychiatry.* 1994;35:711-7.
243. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *American Journal of Psychiatry.* 2006;163(11):1905-17.
244. Rush AJ, Trivedi MH, Wisniewski SR, Stewart JW, Nierenberg AA, Thase ME, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med.* 2006 Mar 23;354(12):1231-42.
245. Sackeim HA. Magnetic stimulation therapy and ECT. *Convuls Ther.* 1994;10(4):255-8.
246. Sackeim HA. Repetitive transcranial magnetic stimulation: What are the next steps? *Biological Psychiatry.* 2000;48(10):959-61.
247. Sackeim HA. Memory and ECT: from polarization to reconciliation. *J ECT.* 2000;16(2):87-96.
248. Sackeim HA, Portnoy S, Neeley P. Cognitive consequences of low-dosage electroconvulsive therapy. *Annals of the New York Academy of Sciences.* 1986;VOL. 462:326-40.
249. Saijo T, Takano A, Suhara T, Arakawa R, Okumura M, Ichimiya T, et al. Effect of electroconvulsive therapy on 5-HT_{1A} receptor binding in patients with depression: a PET study with [¹¹C]WAY 100635. *Int J Neuropsychopharmacol.* Jul;13(6):785-91.
250. Saito S, Takahashi N, Ishihara R, Ikeda M, Suzuki T, Kitajima T, et al. Association study between vesicle-associated membrane protein 2 gene polymorphisms and fluvoxamine response in Japanese major depressive patients. *Neuropsychobiology.* 2006;54(4):226-30.
251. Salinsky MC. A randomized controlled trial of chronic vagus nerve stimulation for treatment of medically intractable seizures. *Neurology.* 1995;45(2):224-30.
252. Santos MA, Rocha FL, Hara C. Efficacy and safety of antidepressant augmentation with lamotrigine in patients with treatment-resistant depression: A randomized, placebo-controlled, double-blind study. *Primary Care Companion to the Journal of Clinical Psychiatry.* 2008;10(3):187-90.
253. Schatzberg AF, Rush AJ, Arnow BA, Banks PL, Blalock JA, Borian FE, et al. Chronic depression: medication (nefazodone) or psychotherapy (CBASP) is effective when the other is not. *Arch Gen Psychiatry.* 2005 May;62(5):513-20.
254. Schneider F, Harter M, Brand S, Sitta P, Menke R, Hammer-Filipiak U, et al. Adherence to guidelines for treatment of depression in in-patients. *Br J Psychiatry.* 2005 Nov;187:462-9.
255. Schneider LS, Sloane RB, Staples FR, Bender M. Pretreatment orthostatic hypotension as a predictor of response to nortriptyline in geriatric depression. *Journal of Clinical Psychopharmacology.* 1986;6(3):172-6.
256. Schweitzer I, Tuckwell V. Risk of adverse events with the use of augmentation therapy for the treatment of resistant depression. *Drug Saf.* 1998 Dec;19(6):455-64.
257. Scott AIF, Freeman CPL. Edinburgh primary care depression study: Treatment outcome, patient satisfaction, and cost after 16 weeks. *British Medical Journal.* 1992;304(6831):883-7.

258. Scott J. Treatment of chronic depression. *New England Journal of Medicine*. 2000;342(20):1518-20.
259. Scott J, Teasdale JD, Paykel ES, Johnson AL, Abbott R, Hayhurst H, et al. Effects of cognitive therapy on psychological symptoms and social functioning in residual. *British Journal of Psychiatry*. 2000;177(NOV.):440-6.
260. Segui J, Lopez-Munoz F, Alamo C, Camarasa X, Garcia-Garcia P, Pardo A. Effects of adjunctive reboxetine in patients with duloxetine-resistant depression: a 12-week prospective study. *J Psychopharmacol*. 2010 Aug;24(8):1201-7.
261. Seth R, Jennings AL, Bindman J, Phillips J, Bergmann K. Combination treatment with noradrenalin and serotonin reuptake inhibitors in resistant depression. *Br J Psychiatry*. 1992 Oct;161:562-5.
262. Shafique S, Dalsing MC. Vagus nerve stimulation therapy for treatment of drug-resistant epilepsy and depression. *Perspect Vasc Surg Endovasc Ther*. 2006 Dec;18(4):323-7.
263. Shuchman M. Approving the vagus-nerve stimulator for depression. *New England Journal of Medicine*. 2007;356(16):1604-7.
264. Simpson KN, Welch MJ, Kozel FA, Demitrack MA, Nahas Z. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. *Adv Ther*. 2009 Mar;26(3):346-68.
265. Sokolski KN. Adjunctive aripiprazole for bupropion-resistant major depression. *Annals of Pharmacotherapy (USA)*. 2008 01/01;42(Feb):1124-9.
266. Solvason HB, Husain M, Fitzgerald PB, Rosequist P, McCall V, Kimball J, et al. TMS in the acute treatment of major depression: Improvements in functional status and quality of life. Society fo Biological Psychiatry Annual Meeting. San Diego, CA 2007.
267. Souza FG, Goodwin GM. Lithium treatment and prophylaxis in unipolar depression: a meta-analysis. *Br J Psychiatry*. 1991 May;158:666-75.
268. Spitzer RL, National Institute of Mental Health (U.S.). User's guide for the structured clinical interview for DSM-III-R: SCID. Washington, DC: American Psychiatric Press 1990.
269. Stanley W, Fleming H. A clinical comparison of phenelzine and electro-convulsive therapy in the treatment of depressive illness. *Br J Psychiatry*. 1962;108:708-10.
270. Stein G, Bernadt M. Lithium augmentation therapy in tricyclic-resistant depression. A controlled trial using lithium in low and normal doses. *Br J Psychiatry*. 1993 May;162:634-40.
271. Steiner M, Radwan M, Elizur A. Failure of L-triiodothyronine (T3) to potentiate tricyclic antidepressant response. *Current Therapeutic Research - Clinical and Experimental*. 1978;23(5 II):655-9.
272. Sterling P. ECT damage is easy to find if you took for it [3]. *Nature*. 2000;403(6767):242.
273. Steuer JL, Mintz J, Hammen CL. Cognitive-behavioral and psychodynamic group psychotherapy in treatment of geriatric depression. *Journal of Consulting and Clinical Psychology*. 1984;52(2):180-9.
274. Stimpson N, Agrawal N, Lewis G. Randomised controlled trials investigating pharmacological and psychological interventions for treatment-refractory depression. *British Journal of Psychiatry*. 2002;181:284-94.
275. Strömngren LS. Unilateral versus bilateral electroconvulsive therapy. Investigations into the therapeutic effect in endogenous depression. *Acta Psychiatrica Scandinavica, Supplement*. 1973;240:8-65.
276. Szabo K, Hirsch JG, Krause M, Ende G, Henn FA, Sartorius A, et al. Diffusion weighted MRI in the early phase after electroconvulsive therapy. *Neurol Res*. 2007 Apr;29(3):256-9.
277. Taylor MA, Abrams R. Short-term cognitive effects of unilateral and bilateral ECT. *British Journal of Psychiatry*. 1985;146(MAR.):308-11.

278. Taylor MP, Reynolds III CE, Frank E, Cornes C, Miller MD, Stack JA, et al. Which elderly depressed patients remain well on maintenance interpersonal psychotherapy alone?: Report from the Pittsburgh Study of Maintenance Therapies in late-life depression. *Depression and Anxiety*. 1999;10(2):55-60.
279. Teasdale JD, Scott J, Moore RG, Hayhurst H, Pope M, Paykel ES. How does cognitive therapy prevent relapse in residual depression? Evidence from a controlled trial. *J Consult Clin Psychol*. 2001 Jun;69(3):347-57.
280. Thase Jr ME, Rush Jr AJ. Treatment-resistant depression. *Treatment-Resistant Depression in Psychopharmacology: The Fourth Generation of Progress*. 1995.
281. Thase ME, Blomgren SL, Birkett MA, Apter JT, Tepner RG. Fluoxetine treatment of patients with major depressive disorder who failed initial treatment with sertraline. *J Clin Psychiatry*. 1997 Jan;58(1):16-21.
282. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *British Journal of Psychiatry*. 2001;178(MARCH.):234-41.
283. Thase ME, Ferguson JM, Lydiard RB, Wilcox CS. Citalopram treatment of paroxetine-intolerant depressed patients. *Depress Anxiety*. 2002;16(3):128-33.
284. Thase ME, Friedman ES, Biggs MM, Wisniewski SR, Trivedi MH, Luther JF, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* 2007;739-52.
285. Thase ME, Greenhouse JB, Frank E, Reynolds CF, 3rd, Pilkonis PA, Hurley K, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. *Arch Gen Psychiatry*. 1997 Nov;54(11):1009-15.
286. Thase ME, Simons AD, McGeary J, Cahalane JF, Hughes C, Harden T, et al. Relapse after cognitive behavior therapy of depression: Potential implications for longer courses of treatment. *American Journal of Psychiatry*. 1992;149(8):1046-52.
287. Thiery M. Clinical trial of the treatment of depressive illness. *BMJ*. 1965;1:881-6.
288. Thomas SA, Lincoln NB. Factors relating to depression after stroke. *Clinical Rehabilitation*. 2004;18(5):589-90.
289. Thomas SA, Lincoln NB. Factors relating to depression after stroke. *British Journal of Clinical Psychology*. 2006;45(1):49-61.
290. Thompson LW, Gallagher D, Breckenridge JS. Comparative effectiveness of psychotherapies for depressed elders. *Journal of Consulting and Clinical Psychology*. 1987;55(3):385-90.
291. Tome MB, Isaac MT, Harte R, Holland C. Paroxetine and pindolol: a randomized trial of serotonergic autoreceptor blockade in the reduction of antidepressant latency. *Int Clin Psychopharmacol*. 1997 Mar;12(2):81-9.
292. Trivedi MH, Fava M, Wisniewski SR, Thase ME, Quitkin F, Warden D, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med*. 2006 Mar 23;354(12):1243-52.
293. Usui C, Doi N, Nishioka M, Komatsu H, Yamamoto R, Ohkubo T, et al. Electroconvulsive therapy improves severe pain associated with fibromyalgia. *Pain*. 2006 Apr;121(3):276-80.
294. Valentine M, Keddie KM, Dunne D. A comparison of techniques in electroconvulsive therapy. *British Journal of Psychiatry*. 1968;114(513):989-96.
295. Van Schaik A, Van Marwijk H, Adèr H, Van Dyck R, De Haan M, Penninx B, et al. Interpersonal psychotherapy for elderly patients in primary care. *American Journal of Geriatric Psychiatry*. 2006;14(9):777-86.
296. Vandoolaeghe E, Maes M, Vandevyvere J, Neels H. Hypothalamic-pituitary-thyroid-axis function in treatment resistant depression. *J Affect Disord*. 1997 Apr;43(2):143-50.
297. Wajima Z, Shiga T, Yoshikawa T, Ogura A, Inoue T, Ogawa R. Propofol alone, sevoflurane alone, and combined propofol-sevoflurane anaesthesia in electroconvulsive therapy. *Anaesth Intensive Care*. 2003 Aug;31(4):396-400.

298. Walker PW, Cole JO, Gardner EA, Hughes AR, Johnston JA, Batey SR, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. *J Clin Psychiatry*. 1993 Dec;54(12):459-65.
299. Weilburg JB, Rosenbaum JF, Biederman J, Sachs GS, Pollack MH, Kelly K. Fluoxetine added to non-MAOI antidepressants converts nonresponders to responders: a preliminary report. *J Clin Psychiatry*. 1989 Dec;50(12):447-9.
300. Weiner RD, Rogers HJ, Davidson JRT, Squire LR. Effects of stimulus parameters on cognitive side effects. *Annals of the New York Academy of Sciences*. 1986;462:315-25.
301. Welch CA, Weiner RD, Weir D. Efficacy of ECT in the treatment of depression: Wave form and electrode placement considerations. *Psychopharmacology bulletin*. 1982;18(1):31-4.
302. Wells KB, Sturm R, Sherbourne CD, Meredith LS. *Caring for Depression*. Caring for Depression. 1996.
303. White PF, Amos Q, Zhang Y, Stool L, Husain MM, Thornton L, et al. Anesthetic considerations for magnetic seizure therapy: a novel therapy for severe depression. *Anesth Analg*. 2006/06/23 ed 2006:76-80, table of contents.
304. Wijkstra J, Burger H, van den Broek WW, Birkenhager TK, Janzing JG, Boks MP, et al. Treatment of unipolar psychotic depression: a randomized, double-blind study comparing imipramine, venlafaxine, and venlafaxine plus quetiapine. *Acta Psychiatr Scand*. 2009/08/22 ed 2010:190-200.
305. Williams N, Simpson AN, Simpson K, Nahas Z. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Hum Psychopharmacol*. 2009/06/16 ed 2009:401-8.
306. Wilson IC, Vernon JT, Guin T. A controlled study of treatments of depression. *J Neuropsychiatry*. 1963;4:331-7.
307. Zanardi R, Artigas F, Franchini L, Sforzini L, Gasperini M, Smeraldi E, et al. How long should pindolol be associated with paroxetine to improve the antidepressant response? *J Clin Psychopharmacol*. 1997 Dec;17(6):446-50.
308. Zarate CA, Kando JC, Tohen M, Weiss MK, Cole JO. Does intolerance or lack of response with fluoxetine predict the same will happen with sertraline? *J Clin Psychiatry*. 1996 Feb;57(2):67-71.
309. Zervas IM, Papakostas YG, Theodoropoulou MA, Dimitrakopoulos C, Vaidakis N, Daras M. Thyrotropin-releasing hormone administration does not affect seizure threshold during electroconvulsive therapy. *J Ect*. 2003 Sep;19(3):136-8.
310. Zyss T. Deep magnetic brain stimulation - the end of psychiatric electroshock therapy? *Medical Hypotheses*. 1994;43(2):69-74.

Appendix H: Studies Recommended for Inclusion by Peer and Public Reviewers

1. American Psychiatric Association. Committee on Electroconvulsive T, Weiner RD. The practice of electroconvulsive therapy: a task force report of the American Psychiatric Association. Washington, D.C.: American Psychiatric Association.

Rationale: This reference is a set of guidelines. Guidelines do not fit the inclusion criteria for appropriate publication types. The guidelines were not included in the analysis of this review.

2. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry*. 2008 Mar;69(3):441-51.

Rationale: This reference was excluded due to a lack of comparison of interventions between groups. All patients participating in the open-label study receive the same intervention.

3. Bajbouj M, Merkl A, Schlaepfer TE, et al. Two-year outcome of vagus nerve stimulation in treatment-resistant depression. *Journal of Clinical Psychopharmacology* 2010 June;30(3):273-81.

Rationale: This reference was excluded for the present analysis due to a lack of comparison of interventions. The study analyzes outcome measures after 3, 12, and 24 months of vagal nerve stimulation.

4. Berman RM, Narasimhan M, Sanacora G, et al. A randomized clinical trial of repetitive transcranial magnetic stimulation in the treatment of major depression. *Biological Psychiatry* 2000 Feb;47(4):332-7.

Rationale: This study is included in the present analysis

5. Clinical Psychiatry Committee. Clinical trial of the treatment of depressive illness: Report to the Medical Research Council *Br Med J* 1965; 1:881-886

Rationale: This reference is from prior to the start date of our search criteria and it is not of a TRD population

6. Demitrack MA, Loo CK, Maixner DF, et al. Transcranial Magnetic Stimulatlin (TMS) in the Treatment of Pharmacoresistant Major Depression: Examination of Cognitive Function During Acute Treatment. Society for Biological Psychiatry Annual Meeting New Research Sessions of the American Psychiatric Association Annual Meeting. Vancouver B.C. San Francisco, CA; 2009.

Rationale: This conference proceeding was included in our analysis as a companion article to O'Reardon, 2007.¹

7. Demitrack MA, Thase ME. Clinical significance of transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant depression: synthesis of recent data. *Psychopharmacol Bull* 2009 July;42(2):5-38.

Rationale: This article was excluded due to the wrong publication type. The study pooled two studies for the analysis. The current review reviewed both studies pooled for analysis for inclusion in this report. One article, O'Reardon, 2007¹ was included in our analysis. The second article, Avery, 2008² was excluded due to no comparison of interventions (see number 2 above).

8. Fava M, Rush AJ, Wisniewski SR, et al. A comparison of mirtazapine and nortriptyline following two consecutive failed medication treatments for depressed outpatients: a STAR*D report. *Am J Psychiatry* 2006:1161-72.

Rationale: This study was included in the Key Question 1b analysis (pharmaceutical interventions). Because it is comparing to pharmaceutical interventions it was only eligible to be included in Key Question 1.

9. George MS, Lisanby SH, Avery D, et al. Daily left prefrontal transcranial magnetic stimulation therapy for major depressive disorder: a sham-controlled randomized trial. *Arch Gen Psychiatry* 2010 May;67(5):507-16.

Rationale: This study was included in the current analysis.

10. George MS, Rush AJ, Marangell LB, et al. A one-year comparison of vagus nerve stimulation with treatment as usual for treatment-resistant depression. *Biol Psychiatry* 2005 Sep 1;58(5):364-73.

Rationale: This study was excluded from Key Question 2 (maintenance of response) analysis due to wrong study design (observational study). The protocol for this review states that only randomized controlled trials and meta-analyses are eligible study designs for this key question.

11. Hausmann A, Pascual-Leone A, Kemmler G, Rupp CI, Lechner-Schoner T, Kramer-Reinstadler K, et al. No deterioration of cognitive performance in an aggressive unilateral and bilateral antidepressant rTMS add-on trial. *Journal of Clinical Psychiatry*. 2004 Jun 2004;65(6):772-82.

Rationale: This study was excluded from analysis as it is not apparent that the population is treatment resistant. The article does not refer to the population as resistant or refractory, nor does it discuss prior treatment failures of the included population.

12. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of clinical benefit with transcranial magnetic stimulation (TMS) in the treatment of pharmacoresistant major depression: Assessment of relapse during a 6-month, multisite, open-label study. *Brain Stimulation*. Netherlands: Elsevier Science 2010:187-99.

Rationale: This article is included in the present analysis.

13. Janicak PG, O'Reardon JP, Sampson SM, et al. Transcranial magnetic stimulation in the treatment of major depressive disorder: a comprehensive summary of safety experience from acute exposure, extended exposure, and during reintroduction treatment. *J Clin Psychiatry* 2008:222-32.

Rationale: This article is included in the present analysis.

14. Janicak PG, Nahas Z, Lisanby SH, et al. Durability of acute response to TMS in the treatment of major depression: relapse during a continuation pharmacotherapy extension study. *Society for Biological Psychiatry Annual Meeting*; 2007 May; San Diego, CA; 2007.

Rationale: This article is included in the present analysis.

15. Kellner CH, Knapp RG, Petrides G, et al. Continuation electroconvulsive therapy vs pharmacotherapy for relapse prevention in major depression: a multisite study from the Consortium for Research in Electroconvulsive Therapy (CORE). *Arch Gen Psychiatry* 2006:1337-44.

Rationale: This study was excluded for not meeting criteria for a treatment resistant population. The article states that only 42.7 percent of a portion of the population rated (using the ATHF) as having had at least one adequate failure. This indicates that 57.3 percent of this population did not have at least one treatment failure. The entire population, therefore, cannot be considered treatment-resistant by this review's definition.

16. Kozel FA, George MS, Simpson KN. Decision Analysis of Cost-Effectiveness of Repetitive Transcranial Magnetic Stimulation Versus Electroconvulsive Therapy for Treatment of Nonpsychotic Severe Depression. *CNS Spectrums*. 2004 Jun 2004;9(6):476-82.

Rationale: This study was excluded from the current analysis due to reporting outcomes that are not of interest for this review. The study reports on an economic decision analysis.

17. Leichsenring F, Rabung S. Effectiveness of long-term psychodynamic psychotherapy: a meta-analysis. *JAMA* 2008 Oct 1;300(13):1551-65.

Rationale: This meta-analysis was not included in the current analysis due to inclusion of the wrong population. It could not be determined that the included populations met the criteria of treatment-resistant depression.

18. Lisanby SH, Husain MM, Rosenquist PB, et al. Daily left prefrontal repetitive transcranial magnetic stimulation in the acute treatment of major depression: clinical predictors of outcome in a multisite, randomized controlled clinical trial. *Neuropsychopharmacology* 2009 Jan;34(2):522-34.

Rationale: This study was excluded for wrong outcome. The study attempts to determine predictors of outcomes which is not an outcome of interest for this review.

19. Lisanby SH, Maddox JH, Prudic J, et al. The effects of electroconvulsive therapy on memory of autobiographical and public events. *Arch Gen Psychiatry* 2000 Jun;57(6):581-90.

Rationale: This study was excluded from the analysis. The study performs its analysis on right unilateral compared to bilateral electrode placement for electroconvulsive therapy. It also compares low versus high electrical dosage. Neither of these comparisons are comparisons of interest for this review.

20. Martis B, Alam D, Dowd SM, et al. Neurocognitive effects of repetitive transcranial magnetic stimulation in severe major depression. *Clin Neurophysiol* 2003 Jun;114(6):1125-32.

Rationale: This article was excluded from this review due to no comparison. This article, although part of a larger randomized controlled trial, only reports on those persons receiving rTMS. The study does not report on any comparison intervention.

21. Nahas Z, Marangell LB, Husain MM, et al. Two-year outcome of vagus nerve stimulation (VNS) for treatment of major depressive episodes. *J Clin Psychiatry* 2005 Sep;66(9):1097-104.

Rationale: This article was excluded from this review due to no comparison. This study analyzes the outcomes from patients treated with vagal nerve stimulation. No other intervention is compared.

22. Nelson AL, Cohen JT, Greenberg D, et al. Much cheaper, almost as good: decrementally cost-effective medical innovation. *Ann Intern Med* 2009 Nov 3;151(9):662-7.

Rationale: This meta-analysis was excluded from the current analysis for wrong outcomes. The meta-analysis reviews cost-utility analyses which are not outcomes of interest for the current review.

23. Nemeroff CB, Heim CM, Thase ME, et al. Differential responses to psychotherapy versus pharmacotherapy in patients with chronic forms of major depression and childhood trauma. *Proc Natl Acad Sci USA* 2003 Nov 25;100(24):14293-6.

Rationale: This study was excluded from the current analysis for including the wrong population. The identical sample used in this study was taken from Keller, 2000³ which was excluded from the current review due to wrong population. The population of the parent study and this subsequent study used as exclusion criteria “absence of a response to three previous adequate trials of at least two different classes of antidepressants or electroconvulsive therapy or to two previous adequate trials of empirical psychotherapy in the three years preceding the study; a serious, unstable medical condition; or a positive urine screen for drugs of abuse. Furthermore, out of the entire study population, 19.7 percent had received no prior treatment for depression.

24. Nierenberg AA, Fava M, Trivedi MH, et al. Comparison of Lithium and T3 Augmentation Following Two Failed Medication Treatments for Depression: A STAR*D Report. *The American Journal of Psychiatry* 2006 Sept;163(9):1519-30.

Rationale: This study was excluded from the current analysis do to wrong intervention. T3 is not an augments of interest for Key Question 1b (pharmaceutical) analysis.

25. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007:1208-16.

Rationale: This study is included in the current analysis. It is not included for Key Question 3 (symptom subtypes). Symptom subtypes represented by standard factor scores measured on the Hamilton Depression Rating Scale are not symptom subtypes of interest for this report.

26. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol* 2009 Dec;120(12):2008-39.

Rationale: This study was not included in the current analysis because it does not represent a publication type of interest. The reference is cited within the text of the current review.

27. Rumi DO, Gattaz WF, Rigonatti SP, et al. Transcranial magnetic stimulation accelerates the antidepressant effect of amitriptyline in severe depression: a double-blind placebo-controlled study. *Biol Psychiatry* 2005 Jan 15;57(2):162-6.

Rationale: This study was not included in the current analysis due to inclusion of wrong population. The study makes no reference to the population as resistant or refractory, nor does it address prior treatment failure.

28. Rush AJ, Marangell LB, Sackeim HA, et al. Vagus nerve stimulation for treatment-resistant depression: a randomized, controlled acute phase trial. *Biological Psychiatry* 2005 Sep 2005;58(5):347-54.

Rationale: This study is included in the current analysis.

29. Rush AJ, Trivedi MH, Wisniewski SR, et al. Bupropion-SR, sertraline, or venlafaxine-XR after failure of SSRIs for depression. *N Engl J Med* 2006 Mar 23;354(12):1231-42.

Rationale: This study was not included for Key Question 1b (Pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.

30. Sackeim HA, Haskett RF, Mulsant BH, et al. Continuation pharmacotherapy in the prevention of relapse following electroconvulsive therapy: a randomized controlled trial. *JAMA* 2001 Mar 14;285(10):1299-307.

Rationale: This study was not included for Key Question 1b (pharmaceutical analysis) because the population did not meet the criteria of 2 or more treatment failures. Key Question 1b required included populations to have 2 or more treatment failures.

31. Sackeim HA, Brannan SK, Rush AJ, et al. Durability of antidepressant response to vagus nerve stimulation (VNS). *Int J Neuropsychopharmacol* 2007 Dec;10(6):817-26.

Rationale: This study was not included in the current analysis because it does not contain a comparison of interest. The study analyzes outcomes after vagal nerve stimulation and compares outcomes between responders and non-responders.

32. Sackeim HA, Prudic J, Devanand DP, et al. A prospective, randomized, double-blind comparison of bilateral and right unilateral electroconvulsive therapy at different stimulus intensities. *Arch Gen Psychiatry* 2000;57(5):425-34.

Rationale: This study was not included in the current analysis because the analysis does not include a comparison of interest. The study compares right unilateral ECT at three different thresholds to bilateral ECT at one threshold. There is no other intervention comparison.

33. Sackeim HA, Prudic J, Fuller R, et al. The cognitive effects of electroconvulsive therapy in community settings. *Neuropsychopharmacology* 2007 Jan;32(1):244-54.

Rationale: This study was not included in the current analysis because the analysis does not include a comparison. The study compares baseline and post-treatment outcomes after electroconvulsive therapy.

34. Simpson KN, Welch MJ, Kozel FA, et al. Cost-effectiveness of transcranial magnetic stimulation in the treatment of major depression: a health economics analysis. *Adv Ther* 2009 Mar;26(3):346-68.

Rationale: This study was not included in the current analysis for reporting outcomes that were not of interest for the current review. The study performs cost-effective analyses. Please note the study is cited in the text of the review.

35. Tew JD, Jr., Mulsant BH, Haskett RF, et al. Relapse during continuation pharmacotherapy after acute response to ECT: a comparison of usual care versus protocolized treatment. *Ann Clin Psychiatry* 2007 Jan-Mar;19(1):1-4.

Rationale: This study was excluded for wrong comparison. In this continuation study which would have been considered for key question 2, the study only compares pharmacotherapy to treatment as usual which is not a comparison of interest for this key question.

36. Thase ME, Friedman ES, Biggs MM, et al. Cognitive therapy versus medication in augmentation and switch strategies as second-step treatments: a STAR*D report. *Am J Psychiatry* 2007:739-52.

Rationale: This study is included in the current analysis.

37. Trivedi MH, Fava M, Wisniewski SR, et al. Medication augmentation after the failure of SSRIs for depression. *N Engl J Med* 2006 Mar 23;354(12):1243-52.

Rationale: This study was excluded for wrong population. This study population did not meet the strict population criteria of Key Question 1b which required the entire population to have failed at least 2 prior treatments.

38. Williams N, Simpson AN, Simpson K, et al. Relapse rates with long-term antidepressant drug therapy: a meta-analysis. *Hum Psychopharmacol* 2009 July;24(5):401-8.

Rationale: This meta-analysis was not included in this review because it included populations that are not treatment-resistant. The authors clearly stated that three of the studies excluded treatment-resistant depression and seven studies had no criteria pertaining to TRD.

39. Efficacy and safety of electroconvulsive therapy in depressive disorders: a systematic review and meta-analysis. *Lancet* 2003 Mar 8;361(9360):799-808.

Rationale: Overall review excluded because populations were not all TRD, but we note that two of the studies from this SER are included in KQ1a.

References

1. O'Reardon JP, Solvason HB, Janicak PG, et al. Efficacy and safety of transcranial magnetic stimulation in the acute treatment of major depression: a multisite randomized controlled trial. *Biol Psychiatry* 2007:1208-16.
2. Avery DH, Isenberg KE, Sampson SM, et al. Transcranial magnetic stimulation in the acute treatment of major depressive disorder: clinical response in an open-label extension trial. *J Clin Psychiatry* 2008 Mar;69(3):441-51.
3. Keller MB, McCullough JP, Klein DN, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. *N Engl J Med* 2000;342(20):1462-70.