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Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics – Update

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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 State Children's Health Insurance Program (SCHIP).

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://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 are essential to the Effective Health Care Program. Please visit the Web site (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.

Acknowledgments

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Contents

Chapter 1. Introduction 17
Background 17
Off-label Conditions 18
Scope and Key Questions 23
The Key Questions 23
Scope 23
Chapter 2. Methods 25
Topic Development 25
Analytic Framework 25
Search Strategy 26
Technical Expert Panel 27
Study Selection 27
Data Extraction 28
Quality Assessment 28
Applicability 29
Rating the Body of Evidence 29
Data Synthesis 32
Efficacy 32
Adverse Events 33
Peer Review and Public Commentary 34
Chapter 3. Results 35
Key Question I. 38
What are the leading off-label uses of atypical antipsychotics in the literature? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials? 38
Key Points 38
Detailed Analysis 39
Discussion 47
Key Question II. 48
What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications, such as depression? 48
Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications? 48
Key Points 48
Detailed Analysis 52
Discussion 104
Key Question III: 108
What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype? 108
Key Points 108
Detailed Analysis 109
Discussion 110
Key Question IV: 110

What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions? ... 110
Key Points ... 110
Detailed Analysis ... 114
Discussion ... 127
Key Question V: ... 128
What is the effective dose and time limit for off-label indications? ... 128
Key Points ... 128
Detailed Analysis ... 128
Discussion ... 134
Chapter 4. Summary and Discussion ... 135
Future Research ... 145
References ... 149
Abbreviations and Acronyms Glossary ... 165

Tables

Table 1. Summary of strength of evidence of efficacy, by drug and condition ... 4
Table 2. Summary update: Efficacy of atypical antipsychotics for off-label use ... 5
Table 3. Summary update: Safety of atypical antipsychotics for off-label use ... 11
Table 4. Grading the strength of a body of evidence: Required domains and their definitions ... 30
Table 5. Large Utilization Studies in the United States ... 42
Table 6. Atypical antipsychotics for ADHD ... 53
Table 7. Generalized Anxiety Disorder – PCTs contributing to analysis ... 54
Table 8. Dementia – PCTs contributing to meta-analyses ... 58
Table 9. Dementia Head-to-head Studies contributing to analysis ... 67
Table 10. Dementia Atypical vs Haloperidol – PCTs contributing to analysis ... 71
Table 11. Depression – Placebo-controlled augmentation trials contributing to HAM-D meta-analysis ... 76
Table 12. Depression – Placebo-controlled augmentation trials contributing to MADRS meta-analysis ... 80
Table 13. Eating Disorder – PCTs contributing to meta-analysis ... 84
Table 14. Atypical antipsychotics for Insomnia - Olanzapine ... 86
Table 15. Atypical antipsychotics for Insomnia - Quetiapine ... 86
Table 16. OCD – PCTs contributing to meta-analysis ... 88
Table 17. Atypical antipsychotics for Personality Disorder ... 91
Table 18. PTSD – PCTs contributing to meta-analyses ... 94
Table 19. Alcohol Abuse – PCTs contributing to meta-analyses ... 100
Table 20. Cocaine – PCTs contributing to meta-analysis ... 102
Table 21. Atypical antipsychotics for Tourette's syndrome ... 103
Table 22. Summary of strength of evidence of efficacy, by drug and condition ... 106
Table 23. Analysis of publication bias ... 107
Table 24. Cardiovascular adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo ... 115

Table 25. Neurological adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo 116
Table 26. Endocrine adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo 117
Table 27. Urinary symptoms among dementia patients – Atypical Antipsychotics Compared to Placebo 117
Table 28. Adverse events in large observational studies 119
Table 29. Appetite or weight increase in other conditions – Atypical Antipsychotics Compared to Placebo 123
Table 30. Endocrine and other metabolic lab abnormalities in other conditions – Atypical Antipsychotics Compared to Placebo 124
Table 31. Neurological adverse events in other conditions – Atypical Antipsychotics Compared to Placebo 124
Table 32. Summary update: Efficacy of atypical antipsychotics for off-label use 137
Table 33. Summary update: Safety of atypical antipsychotics for off-label use 142

Figures

Figure 1. Analytic Framework for Comparative Effectiveness Review: Off-label Uses of Atypical Antipsychotics 26
Figure 2. Literature Flow 36
Figure 3. Anxiety % Responders on Hamilton Anxiety Scale 56
Figure 4. Dementia Placebo Comparisons – Total/ Global Scores 64
Figure 5. Dementia Placebo Comparisons – Psychosis 65
Figure 6. Dementia Placebo Comparisons - Agitation 66
Figure 7. Dementia Head-to-head Studies Olanzapine or Quetapine vs Risperidone – Total/global scores 68
Figure 8. Head-to-head Studies: Olanzapine or Quetapine vs. Risperidone – Psychosis 69
Figure 9. Dementia Head-to-head Studies: Olanzapine or Quetapine vs Risperidone - Agitation70
Figure 10. Dementia: Atypical vs Haloperidol - Total/Global Scores 72
Figure 11. Dementia: Atypical vs Haloperidol - Agitation 73
Figure 12. Depression – HAM-D % Remitted 78
Figure 13. Depression – HAM-D % Responded 79
Figure 14. Depression – MADRS % Remitted 82
Figure 15. Depression – MADRS % Responded 83
Figure 16. Eating Disorders – BMI 85
Figure 17. OCD – Responders improving 25-35% on YBOCS 90
Figure 18. PTSD – By Drug – Difference in CAPS score 95
Figure 19. PTSD – By Combat Status – Difference in CAPS score 96
Figure 20. PTSD – By Time – Difference in CAPS score 97
Figure 21. Substance Abuse – Alcohol Complete Abstinence 101
Figure 22. Cocaine – ASI Drug Composite 102
Figure 23. Dementia PCTs – with dose comparisons – Total/global scores 129
Figure 24. Dementia: PCTs with dose comparisons - Psychosis 130
Figure 25. Dementia: PCTs with dose comparisons - Agitation 131
Figure 26. Depression – MADRS % Remitted – Dose 132

Figure 27. Depression – MADRS % Responded – Dose..... 133

Appendixes

Appendix A: Literature Search Strategies
Appendix B: Data Collection Forms
Appendix C: Previously Published Meta-Analyses
Appendix D: Evidence Tables
Appendix E: List of Rejected Studies
Appendix F: Peer Reviewers/Acknowledgments (to be added for final report)
Appendix G: Adverse Events Analyses

Appendices and evidence tables are provided electronically at
http:…….

Efficacy and Comparative Effectiveness of Off-Label Use of Atypical Antipsychotics-update

Executive Summary

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary will be available at www.effectivehealthcare.ahrq.gov/reports/final.cfm

Background

Antipsychotics medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These medications are commonly divided into two classes, reflecting two waves of historical development: the conventional antipsychotics and the atypical. The conventional antipsychotics served as the first successful pharmacologic treatment for primary psychotic disorders such as schizophrenia. Having been widely used for decades, the conventional antipsychotics also produced various side effects requiring additional medications, which spurred the development of the atypical antipsychotics.

Currently, nine atypical antipsychotic drugs have been approved by FDA: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. These drugs have been used off-label (i.e. for indications not approved by the FDA) for the treatment of various psychiatric conditions. While it is legal for a physician to prescribe drugs in such a manner, it is illegal for the manufacturer to actively promote such use.

A 2006 study on Efficacy and Comparative Effectiveness of Off-label Use of Atypical Antipsychotics reviewed the scientific evidence on the safety, efficacy, and effectiveness for off-label uses. (Clozapine was excluded because of its association with a potentially fatal blood disorder of bone marrow suppression and requires frequent blood tests for safety monitoring.) The 2006 study examined 84 published studies on atypicals and found that the most common off-label uses of the drugs were for treatment of depression, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), personality disorders, Tourette's syndrome, autism, and agitation in dementia. It concluded that with few exceptions, there was insufficient high strength evidence to reach conclusions about the efficacy of any off-label uses of these medications. It also found strong evidence that atypicals are associated with increased risk of

adverse events such as significant weight gain, sedation, and, among the elderly, increased mortality. Future research areas suggested by the report include safe treatment for agitation in dementia, association between the increased risk of death and antipsychotics drugs, and comparison of the development of adverse effects between patients taking atypical antipsychotics and those taking conventional antipsychotics.

Since publication of that report, important changes have occurred that could make it out of date. Studies have been published on new off-label uses, such as treatment of eating disorders, insomnia, attention-deficit hyperactivity disorder (ADHD), anxiety, and substance abuse. New or increased adverse effects of off-label indications have been observed and new atypicals (asenapine, iloperidone, and paliperidone) have been approved by FDA for the treatment of schizophrenia and bipolar disorder. In addition, the following previously off-label uses have been approved for on-label use by the FDA:

- Quetiapine and quetiapineXR (extended release) as monotherapy in bipolar depression
- Quetiapine XR as augmentation for major depressive disorder (MDD)
- Aripiprazole as augmentation for MDD
- Olanzapine / fluoxetine combination for MDD
- Olanzapine / fluoxetine combination for bipolar depression
- Risperidone for autism spectrum disorders.

An update is clearly needed to better understand the trends in off-label use and the associated risks and benefits. Further, a number of issues remain unclear due to insufficient information in the previous report: subpopulations (i.e. race / ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. This update will try to address these issues.

This report covers the following off-label uses of atypical antipsychotic medications: anxiety, ADHD, dementia and severe geriatric agitation, major depressive disorder (MDD), eating disorders, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. Autism, included in the original systematic review, is now reviewed in a study on the comparative effectiveness of typical and atypical antipsychotics for on-label indications, conducted by another EPC.

This report addresses the following key questions:

Key Question 1: What are the leading off-label uses of atypical antipsychotics in the literature? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question 2: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications, such as depression?

Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications?

Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question 5: What is the effective dose and time limit for off-label indications?

Conclusions

Key Question 1: What are the leading off-label uses of atypical antipsychotics in the literature? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Atypicals have been studied as off label treatment for the following conditions: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, OCD, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.

Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s; risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.

Utilization studies identified covered mostly the period from 1996 to 2004; only a few were conducted after 2005 FDA and Health Canada warnings on possible severe adverse events in the elderly. However, one recent study indicated that the 2005 regulatory warning was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. However, the prevalence of off-label indications of atypical drugs remains high.

No off-label use of the newly approved atypicals (asenapine, iloperidone, and paliperidone) was reported in the utilization literature.

Key Question 2: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics, for off-label indications, such as depression? Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications?

The efficacy results are summarized in Table 1 below. It is important to note that no trials of the three most recently FDA approved atypicals (asenapine, iloperidone, and paliperidone) were found for off-label use. Cells shaded in green indicate areas with the strongest evidence of efficacy, followed by the areas in blue. White areas containing circles indicate areas where no clinical trials exist. Brown and pink areas indicate areas where evidence of inefficacy exists.

Table 1. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety – generalized anxiety disorder	O	+	++	-	-
Anxiety – social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder -no co-occurring disorders	O	O	O	+	O
Attention Deficit/Hyperactivity Disorder -bipolar children	-	O	O	O	O
Attention Deficit/Hyperactivity Disorder -mentally retarded children	O	O	O	+	O
Dementia overall	++	++	++	++	O
Dementia psychosis	++	+	+	++	O
Dementia agitation	++	++	+	++	O
Depression -MDD augmentation of SSRI / SNRI	++	+	++	++	+
Depression -MDD: Monotherapy	O	--	O	O	O
Eating Disorders	O	--	O	O	O
Insomnia – NO RCTS FOUND					
Obsessive Compulsive Disorder -augmentation of SSRI	O	+	++	++	-
Obsessive Compulsive Disorder -augmentation of citalopram	O	O	+	+	O
Personality Disorder -borderline	+	+-	+	O	-
Personality Disorder -schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder	O	+	O	++	O
Substance Abuse - alcohol	--	-	-	O	O
Substance Abuse - cocaine	O	-	O	-	O
Substance Abuse - methamphetamine	-	O	O	O	O
Substance Abuse - methadone clients	O	O	O	-	O
Tourette's Syndrome	O	O	O	+	-

++: moderate or high evidence of efficacy
+ : low or very low evidence of efficacy
+- : mixed results
- : low or very low evidence of inefficacy
-- : moderate or high evidence of inefficacy
O : no trials

Table 2 below shows how our 2010 efficacy findings compare with those of our original CER submitted to AHRQ in 2006. The evidence that atypicals have efficacy in treating symptoms of dementia has increased in the past few years; this evidence must be weighed against possible harms described in Key Question Four below. Evidence of efficacy as augmentation for major depressive disorder (MDD) and obsessive compulsive disorder (OCD) patients who have not responded adequately to SSRIs / SNRIs has also increased.

Table 2. Summary update: Efficacy of atypical antipsychotics for off-label use

Usage	Strength of evidence	2006 Findings	2010 Findings	2010 Conclusions
Dementia	High	A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.	Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, quetiapine, and risperidone were superior to placebo as measured by total scores on BEHAVE-D, BPRS, and NPI. Psychosis – In our meta-analysis aripiprazole and risperidone were superior to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for olanzapine and quetiapine did not meet conventional levels of statistical significance. Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Results for quetiapine did not meet conventional levels of statistical significance. Two head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, quetiapine and risperidone **have efficacy** as treatment for behavioral symptoms of dementia. There are no trials of ziprasidone for this use.

Depression – MDD: augmentation of SSRI / SNRI	Moderate – quetiapine, risperidone, aripiprazole Low – olanzapine, ziprasidone	Three trials assessed the combination of olanzapine and fluoxetine , one trial each assessed augmentation of various SRIs with risperidone, ziprasidone, and quetiapine, and one study assessed adding risperidone versus olanzapine to SSRI. The combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine. The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.	We conducted a meta-analysis using "response" to treatment as outcome. A responder was defined as someone who had at least a 50% reduction in depression score from randomization to follow up. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole or quetiapine was significantly higher than those taking placebo. Risperidone and ziprasidone were included in one trial each; both trials reported the drug superior to placebo. One study compared olanzapine plus fluoxetine with olanzapine or fluoxetine alone. No placebo was used. Mean change in MADRS score was significantly higher with olanzapine plus fluoxetine. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**
Depression – MDD: Monotherapy	Moderate	The three olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	One new trial reported quetiapine increased time to next depressed event compared to placebo.	Same as 2006: Olanzapine **does not have efficacy** as monotherapy for major depressive disorder.

Obsessive compulsive disorder – augmentation of SSRI	Moderate – Quetiapine, risperidone Low - olanzapine	12 trials used risperidone, olanzapine, and quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	Two new trials of quetiapine were added to those included in our 2006 meta-analysis. The new results echoed those of our original CER, finding quetiapine and risperidone superior to placebo, as measured by changed in the Yale Brown Obsessive Compulsive Scale (YBOCS). There were too few studies (two) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more effective than ziprasidone as SSRI augmentation. One new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in YBOCS score, while clomipramine did not.	Quetiapine and risperidone **have efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also **have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine for this purpose.
Obsessive compulsive disorder – augmentation of citalopram	Low- quetiapine Very low - risperidone	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 days v. 85 days)	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to YBOCS and CGI-I scores.	Quetiapine **is efficacious** as augmentation to citalopram in OCD patients. Risperidone may also be **efficacious.**
Post traumatic stress disorder	Moderate - risperidone	Four trials of risperidone and two trials of olanzapine, each of at least 6 week's duration, treated patients with PTSD. Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	Three new trials of risperidone were found, allowing us to conduct a meta-analysis using the Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Personality disorders - borderline	Moderate – aripiprazole Low – olanzapine, quetiapine, ziprasidone	Three trials provide evidence that olanzapine is superior to placebo & may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Aripiprazole was superior to placebo in one small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. Two new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. One new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Trials using atypical antipsychotics for treatment of borderline personality disorder (BPD) have shown mixed results. Due to heterogeneity of outcomes, we could not perform a meta-analysis. Olanzapine had **mixed results** in 7 trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Personality disorders - schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's syndrome	Low	Risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	No additional trials.	Same as 2006: Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Eating disorders	Moderate	Not covered.	Four trials of olanzapine were found; three reporting Body Mass Index (BMI) could be pooled. There was no difference in change in BMI at either one or three months compared to placebo.	Olanzapine **has no efficacy** in increasing body mass in eating disorder patients.
Anxiety	Moderate	Not covered.	Three placebo-controlled trials of quetiapine for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder

Attention deficit / hyperactivity disorder – no co-occurring disorders	Low	Not covered.	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale – Parent version (CAS-P).	Risperidone may be **efficacious** in treating children with ADHD with no serious co-occurring disorders.
Attention deficit / hyperactivity disorder - mentally retarded children	Low	Not covered.	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Attention deficit / hyperactivity disorder - bipolar children	Low	Not covered.	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Substance abuse - alcohol	Moderate – aripiprazole Low – quetiapine	Not covered.	Two trials of aripiprazole and one of quetiapine reported % of patients completely abstinent during follow-up. In our pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse / dependence. Quetiapine may also be **inefficacious.**
Substance abuse - cocaine	Low	Not covered.	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse / dependence. Risperidone may also be **inefficacious.**
Substance abuse – meth-amphetamine	Low	Not covered.	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse / dependence.
Substance abuse – methadone clients	Low	Not covered.	One trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance.
Insomnia	Very low.	Not covered.	No trials found. Two observational studies of olanzapine and four of quetiapine found promising improvements in sleep quality and sleep onset.	Olanzapine and quetiapine **may have efficacy** in improving insomnia symptoms.

Key Question 3: What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

There are insufficient data regarding efficacy, effectiveness, and harms, to determine what subset of the population would potentially benefit from off-label uses of atypicals. Only one study conducted a subgroup analysis by gender; there were no studies that stratified by racial or ethnic group. Although many studies specified age in their inclusion criteria, no studies stratified results by age.

Examination of the literature for differing efficacy of atypicals by clinical subsets did not reveal studies reporting subgroup analyses. Our own meta-analysis found efficacy for combat-related PTSD in men but not for PTSD in civilian women. Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any other condition.

Key Question 4: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Table 3 compares the most important findings regarding adverse events, by age group and study design.

Table 3. Summary update: Safety of atypical antipsychotics for off-label use

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Weight gain – Elderly patients	Greater weight gain for olanzapine patients than those taking quetiapine or risperidone, according to one large trial (CATIE-AD). Patients taking any of these three drugs gained more weight than placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone, according to our meta-analysis.
Weight gain – Adults 18 - 64	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone, according to our meta-analysis.
Weight gain – Children & adolescents	No evidence reported.	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in our meta-analysis. No difference in one small PCT of ziprasidone.
Mortality - Elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Five large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Three of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we can not make conclusions regarding safety here.
Endocrine / diabetes – Elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored study of olanzapine patients.

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Endocrine / diabetes – Adults 18 - 64	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in quetiapine in five pooled PCTs. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in five pooled PCTs; however, the pooled odds ratio was elevated at 1.40 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA - Elderly patients	No evidence reported.	No difference of risk by whether the patients used a conventional, atypical, or no antipsychotics therapy, according to a large study of Veterans Administration and Medicare patients. The only risk was in patients with the vascular dementia subtype who received risperidone; they had a decreased risk of CVA compared to haloperidol, whereas olanzapine and quetiapine did not.	More common in risperidone patients according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine according to five PCTs pooled by the manufacturer.
EPS - Elderly patients	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported.	More common in patients taking aripiprazole and risperidone, according to our meta-analysis. Quetiapine was not associated with an increase. More common in olanzapine in one PCT.
EPS – Adults 18 - 64		Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone according to our meta-analysis.

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Sedation – Adults, elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant. In adults 18 – 64, more common in patients taking quetiapine than patients taking risperidone in two trials.	No evidence reported.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone, according to our meta-analysis.
Sedation – Children and adolescents		No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

Key Question 5: What is the effective dose and time limit for off-label indications?

There are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum dose needed. According to a meta-analysis we conducted using the percentage of remitters and responders according to the MADRS as outcome, 150 mg quetiapine daily augmentation has equal efficacy as augmentation with 300 mg for patients with MDD who respond inadequately to SSRIs. More trials examining different doses of other atypicals for MDD would help guide clinicians in treating this population. In addition, more dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder would allow for pooling and comparison of results.

Though there is some trial data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of reported follow-up time. It is likely that trials are designed such that follow-up outcomes are measured (and reported) at a sufficient length of time to see some pharmacological effect.

Remaining Issues

The overarching finding of this review is that although atypical antipsychotic medications are being used for a large number of off-label indications, we were able to find moderate to strong evidence of efficacy for only a few of the drugs and for only a few of the off-label indications. Most of the evidence is for the drugs risperidone, olanzapine, and quetiapine, for the off-label indications of dementia, depression, and obsessive-compulsive disorder. For the newly approved atypicals (asenapine, iloperidone, and paliperidone), we found no clinical trials assessing their use for any off-label condition, and for some off-label uses, we found no or only a small number of trials. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label uses suggests that efficacy differs between drugs, meaning that the assumption of a "class effect" for atypical antipsychotics may be unwarranted. This means that each drug requires its own evaluation of efficacy for each off-label indication, which is a large task; and then drugs demonstrated to be efficacious will need to be compared in head-to-head in trials.

There is almost no existing evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or other comorbidities. In addition, existing evidence about the role of baseline severity of disease is too heterogeneous to allow us to draw conclusions. In future research, standardized measures of disease severity might allow for greater knowledge of the patient populations who would benefit from treatment with atypical agents.

Regarding adverse effects of the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event. It would facilitate assessments of comparative effectiveness if future studies contained a standardized list of assessed side effects. As many trials report only those effects observed, we are unable to compare between trials for many of the side effects.

Another area where clinical guidance is needed is in the dosages required to achieve effects in off-label indications. The dosages used in off-label indications varied from those used in on-

label indications. However, there were few trials that looked at a comparison of dosage effectiveness. As populations of patients and the measures used to evaluate them often differed between trials, a dosage comparison across trials was generally not possible. More research, examining differing dosages within the same population, is required in order to guide clinicians in the appropriate doses to prescribe. A similar issue is that of treatment length. More research examining responses at various time points would be helpful in determining how long treatment is required. Given the risk of side effects when using these agents, clinicians need to know when a result is expected to prevent continuing an inefficacious agent, unnecessarily.

Newer agents, such as asenapine, iloperidone, and paliperidone cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence to date does not support that there is a general "class effect" in terms of either efficacy or harm for most off-label indications. Trials assessing the newer agents' efficacy and safety are necessary if they are to be used off-label for any of the above treatment areas.

Chapter 1. Introduction

Background

Antipsychotics medications are approved by the U.S. Food and Drug Administration (FDA) for treatment of schizophrenia and bipolar disorder. These medications are commonly divided into two classes, reflecting two waves of historical development: the conventional antipsychotics and the atypical. The conventional antipsychotics served as the first successful pharmacologic treatment for primary psychotic disorders such as schizophrenia. Having been widely used for decades, the conventional antipsychotics also produced various side effects requiring additional medications, which spurred the development of the atypical antipsychotics.

Currently, nine atypical antipsychotic drugs have been approved by FDA: aripiprazole, asenapine, clozapine, iloperidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. These drugs (except for the three recently approved ones - asenapine, iloperidone, and paliperidone) have been studied for off-label use in several conditions. A 2006 study[1] on Efficacy and Comparative Effectiveness of Off-label Use of Atypical Antipsychotics reviewed the scientific evidence on the safety, efficacy, and effectiveness for off-label uses. Clozapine was excluded because of its association with a potentially fatal blood disorder of bone marrow suppression and requires frequent blood tests for safety monitoring. Rarely used, except for treatment of schizophrenia, the drug has proven refractive to other treatment. The 2006 study examined 84 published studies on atypical antipsychotics and found that the most common off-label uses of the drugs were treatment of depression, obsessive-compulsive disorder, posttraumatic stress disorder, personality disorders, Tourette's syndrome, autism, and agitation in dementia. It concluded that with few exceptions, there was insufficient high-quality evidence overall to reach conclusions about the efficacy of any off-label indications of these medications. It also found strong evidence that atypical antipsychotics can increase chances of adverse events such as significant weight gain, sedation, and gastrointestinal problems. Future research areas suggested by the study include safe treatment for agitation in dementia, association between the increased risk of death and antipsychotics drugs, and comparison of the development of adverse effects between patients taking atypical antipsychotics and those taking conventional antipsychotics.

Since publication of that report, important changes have occurred that could make it out of date. Studies have been published on new off-label uses, such as treatment of eating disorders, insomnia, attention-deficit hyperactivity disorder (ADHD), anxiety, and substance abuse. New or increased adverse effects of off-label indications have been observed and new atypicals (asenapine, iloperidone, and paliperidone) have been approved by FDA for the treatment of schizophrenia and bipolar disorder. In addition, the following previously off-label uses have been approved for on-label use by the FDA:

- Quetiapine and quetiapineXR (extended release) as monotherapy in bipolar depression
- Quetiapine XR as augmentation for major depressive disorder (MDD)
- Aripiprazole as augmentation for MDD
- Olanzapine / fluoxetine combination for MDD

- Olanzapine / fluoxetine combination for bipolar depression
- Risperidone for autism spectrum disorders.

An update is clearly needed to better understand the trend of off-label use and the risks and benefits associated with off-label use. Further, a number of issues remain unclear due to insufficient information in the previous report: subpopulations (i.e. race / ethnicity, gender) that would benefit most from atypical antipsychotics, appropriate dose, and time needed to see clinical improvement. This update will try to address these issues.

Off-label Conditions

The present study covers the following off-label uses of atypical antipsychotic medications: anxiety, attention-deficit hyperactivity disorder (ADHD), dementia and severe geriatric agitation, depression, eating disorder, insomnia, obsessive-compulsive disorder (OCD), posttraumatic stress disorder (PTSD), personality disorders, substance abuse, and Tourette's syndrome. Autism (included in the original systematic review) will be reviewed in a study on the comparative effectiveness of typical and atypical antipsychotics for on-label indications, conducted by another EPC.

Anxiety. Anxiety disorders include a number of disorders where the primary feature is abnormal or pathological fear and anxiety. Major types of disorders in this category include acute stress disorder, agoraphobia (with or without a history of panic disorder), generalized anxiety disorder (GAD), OCD, panic disorder (with or without agoraphobia), specific phobias (including social phobia), and PTSD. We will report OCD and PTSD separately.

While anxiety is a normal reaction to stress, when it becomes an excessive, irrational dread of everyday situations, it is considered a disabling disorder.[2] About 40 million American adults age 18 years and older (about 18%) suffer from anxiety disorders in a given year.[3] Anxiety disorders can be treated with medication (e.g., antidepressants such as selective serotonin reuptake inhibitors or SSRIs, tricyclics), specific types of psychotherapy, or both.[4]

The most common anxiety disorder treated with atypicals is GAD. GAD is characterized by at least 6 months' persistent and excessive anxiety and worry. People with GAD cannot relax, cannot control the worry, startle easily, can be irritable, and have difficulty concentrating. GAD affects about 6.8 million American adults;[3] and more women suffer from GAD than men.

Attention-Deficit Hyperactivity Disorder (ADHD). Attention-deficit hyperactivity disorder (ADHD or AD/HD) is a neurobehavioral developmental disorder. The DSM-IV-TR recognizes three major subtypes of ADHD: predominantly inattentive subtype, predominantly hyperactive-impulsive subtype, and combined inattentive/hyperactive-impulsive subtype. Inattention, hyperactivity, and impulsivity are the key features of ADHD. To be diagnosed, one must have six (or more) of the inattention symptoms or six (or more) of the hyperactivity-impulsivity symptoms that have persisted for at least 6 months; some impairment from the symptoms must be present in at least two settings (e.g., at home and at school/work); some symptoms that cause impairment must be present before age 7; the symptoms must be severe enough to be considered maladaptive, be inconsistent with the patient's level of development, and not be exclusively due to another condition.

Although the causes of ADHD are unclear, there is evidence suggesting that genes play a large role.[5] Other social or environmental factors such as alcohol use during pregnancy may contribute to ADHD.[6] Treatments for ADHD include medication, psychotherapy, educational interventions, or a combination of treatments. While ADHD is the most common disorder diagnosed in school-age children, it can continue through adolescence and adulthood, and is no longer considered only a childhood disorder.

Dementia and Severe Geriatric Agitation. Dementia is a disorder of acquired deficits in more than one domain of cognitive functioning. These domains are memory, language production and understanding, naming and recognition, skilled motor activity, and planning and executive functioning. The most common dementias – Alzheimer's and vascular dementia - are distinguished by their cause. Alzheimer's dementia occurs with an insidious onset and continues on a degenerative course to death after 8 to10 years;[7] the intervening years are marked by significant disturbances of cognitive functioning and behavior, with severe debilitation in the ability to provide self-care. Vascular dementia refers to deficits of cognitive functioning that occur following either a cerebrovascular event – a stroke – leading to a macrovascular dementia, or, alternatively, more diffusely located changes in the smaller blood vessels, leading to a microvascular dementia. These (and other) dementia types commonly co-occur. Psychotic symptoms are frequent among dementia patients and include auditory hallucinations, believing that one's personal belongings have been stolen, or believing that unknown others are cohabiting with the patient (phantom boarders). Although the cognitive deficits can be severe, it is the behavioral disturbances (such as yelling or combativeness with caregivers) that typically interfere with independent living and necessitate placement in a nursing home.

Management of dementia patients includes both behavioral and psychopharmacologic interventions.[8] Although behavioral interventions are commonly used with dementia patients, they require the presence of trained caregivers. Psychopharmacologic treatments developed specifically for dementia include acetylcholinesterase inhibitors, which attempt to compensate for the loss of neurons that produce the neurotransmitter acetylcholine by inhibiting the enzyme responsible for its degradation. Antipsychotics, including the atypicals, have been used to control both psychotic symptoms and severe behavioral agitation in dementia.

Depression. Depression refers to a potentially severe episodic disturbance of mood, with a constellation of low mood, inability to experience pleasure, sleep and appetite disturbances, loss of energy, difficulty concentrating, thoughts of guilt, worthlessness, and hopelessness, and suicidal ideation.[9] Depression is best thought of as a symptom cluster that can appear in several different psychiatric disorders. These disorders are unipolar depression, bipolar depression, major depression with psychotic features, and depression occurring during psychotic disorders, such as schizophrenia or schizoaffective disorder. (Full descriptions of the diagnostic criteria for these disorders and others discussed in this report can be found in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders, the DSM-IV-TR.)[10]

Unipolar depression refers to major depressive disorder and is defined by episodes of at least a majority of the above symptoms lasting at least two weeks. A particularly severe form of major depressive disorder occurs when the depression is accompanied by psychotic symptoms such as auditory hallucinations. Current treatment guidelines for the pharmacologic treatment of major depression are expressed algorithmically as a flowchart, with later steps tried after the

failure of the earlier steps.[11] Failure may occur for a variety of reasons, including intolerable side effects or lack of improvement after treatment of an appropriate duration. The mainstays of treatment are the antidepressants, including the serotonin reuptake inhibitors (SRIs), including citalopram, escitalopram, fluoxetine, paroxetine, and sertraline; the tricyclic antidepressants, including amitriptyline, imipramine, nortriptyline, and desipramine; and other drugs with dual reuptake inhibition or other mechanisms, including bupropion, duloxetine, mirtazapine, and venlafaxine. Other treatments used include augmenting agents, medications that are not themselves antidepressants, but that speed or improve the antidepressant activity; various psychotherapies; and electroconvulsive therapy. Because of their serotonergic effects, the atypical antipsychotics have been tested as augmenting agents. For depression with psychotic features, the recommended psychopharmacologic treatment, which consists of the simultaneous use of antidepressants and antipsychotics - most often atypical antipsychotics has been advocated.[11-12]

Eating Disorders. Eating disorders are a group of conditions characterized by severe disturbances in eating behavior. Disorders in this category include anorexia nervosa (refusing to maintain a minimally normal body weight) and bulimia nervosa (recurrent binge eating followed by compensatory behaviors such as self-induced vomiting).

DSM-IV-TR criteria[10] for anorexia nervosa include a refusal to maintain body weight at or above a minimally normal weight for age and height, intense fear of gaining weight, three consecutive missed periods, and either refusal to admit the seriousness of the weight loss, or undue influence of shape or weight on one's self image, or a disturbed experience in one's shape or weight. Criteria for bulimia nervosa include recurrent binge eating and inappropriate compensatory behavior in order to prevent weight gain at least twice a week for 3 months, and self-evaluation unduly influenced by body shape and weight.

Causes of eating disorders are poorly understood. Eating disorders usually begin in late adolescence or early adult life, and affect both men and women, although women and girls are much more likely than men and boys to develop an eating disorder.[13] Eating disorders are treatable with medications, nutritional counseling, and psychotherapy.[13]

Insomnia. Insomnia is one type of sleep disorder, characterized by persistent difficulty falling asleep and/or difficulty staying asleep. DSM-IV-TR[10] organizes the sleep disorders into four major sections (primary sleep disorders, sleep disorder related to another mental disorder, sleep disorder due to a general medical condition, and substance-induced sleep disorder). This review defines insomnia broadly and covers all of the four types.

Causes of insomnia are various, including medications, pain from any injury, hormone shifts, mental disorders, restless legs syndrome, poor sleep hygiene (e.g., noise), medical conditions (e.g., hyperthyroidism), etc.[14] Criteria for a diagnosis of primary insomnia include: difficulty initiating or maintaining sleep, or nonrestorative sleep for at least one month; the disturbance must cause significant distress or impairment in social, occupational, or other important functions; the disturbance does not occur exclusively during the course of another mental or medical disorder and is not due to the direct physiological effects of alcohol, medication, or other substances.[10]

Obsessive-Compulsive Disorder (OCD). The essential features of obsessive-compulsive disorder (OCD) are obsessions (repetitive, intrusive, unwanted thoughts, impulses, or images) and compensatory compulsive behaviors that reduce or remove the distress caused by the obsessions. A common example would involve obsessions about fears of contamination by dirt or germs, which give rise to compulsions to wash one's hands excessively.[15] The distress caused by the obsessions, and the time devoted to, or the dysfunction caused by, the compulsions can lead to serious psychiatric morbidity. Standard treatments include psychopharmacologic approaches using the serotonin reuptake inhibitors (SRIs), such as fluoxetine, and cognitive-behavioral therapy, which promotes a kind of learning through exposure to the feared or unpleasant stimulus and prevention of the compulsive response. Limited response to both treatments is common, and various psychopharmacologic agents, including the atypical antipsychotics, have been tested for their ability to augment SRIs.

Posttraumatic Stress Disorder (PTSD). Posttraumatic Stress Disorder (PTSD) describes the development of characteristic disabling symptoms following exposure to trauma such as war or rape. These symptoms are grouped into three clusters: re-experiencing (nightmares, flashbacks), avoidance and numbing (avoidance of reminders of the trauma, inability to recall the trauma, feelings of detachment, restriction of emotion), and increased arousal (anger, problems with concentration, hypervigilance, exaggerated startle response).[16] The symptoms of PTSD span diverse psychiatric categories, and include mood, anxiety, and psychotic symptoms (including auditory hallucinations, suspicion, dissociation, and emotional withdrawal). Treatment of PTSD involves medications that address each of these classes of symptoms (including atypical antipsychotics) and cognitive-behavioral and other psychotherapies.

Personality Disorders. A Personality Disorder is "an enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture, is pervasive and inflexible, has an onset in adolescence or early adulthood, is stable over time, and leads to distress or impairment."[10] The DSM-IV-TR defines ten such disorders. Optimal treatment of such disorders is not well understood, although some of the disorders are the focus of active research. Because of the long-term nature of the disorders, they are often treated through psychotherapy in an attempt to facilitate long-term personality change, while psychiatric medications are thought to play a role in moderating some of the symptomatic manifestations. Only two personality disorders have been treated in clinical trials with atypical antipsychotics: schizotypal personality disorder (SPD) and borderline personality disorder (BPD).

SPD is defined by pervasive deficits in interpersonal relationships, cognitive and perceptual disturbances, and eccentric behavior. The perceptual and behavioral changes often appear similar to a mild form of schizophrenia, and there is some evidence of familial aggregation of SPD in relatives of those with schizophrenia.[17] Because of this connection, treatment with atypical antipsychotics has been tried.

BPD's essential characteristic is instability in interpersonal relationships, self-image, and mood, along with impulsive behavior, intense anger, and recurrent suicidal gestures or attempts. There are often severe dissociative symptoms and paranoid ideation, which may occur or worsen with stress. BPD is a significant cause of psychiatric morbidity, and, because of the increased risk for suicide, mortality. Effective treatment of BPD is an area of active research. The cornerstone of treatment is psychotherapy of various kinds, with dialectical behavior therapy and

mentalization-based therapy, among others, having shown some efficacy in clinical trials.[18] Psychiatric medications are also commonly used, to treat both comorbid conditions, such as mood disorders, and the symptoms of BPD, although the evidence supporting such use is not strong. Because of the occurrence of psychotic symptoms, and because atypical antipsychotics have mood stabilizing properties, they have been tried in the treatment of BPD.

Substance Abuse. The present report covers the substance use disorders (abuse and dependence). Substances reviewed in this report include alcohol, cocaine, marijuana, heroin, ecstasy, methamphetamine, and opioids. Caffeine or nicotine dependence is not included in the current review.

When the individual continues use of the substance despite significant problems related to the substance, substance dependence may be diagnosed. According to DSM-IV-TR,[10] to be diagnosed as substance dependence, three (or more) of the following must be present within a 12-month period: (1) tolerance; (2) withdrawal; (3) the substance is often taken in larger amounts or over a longer period than was intended; (4) there is a persistent desire or unsuccessful efforts to cut down or control substance use; (5) a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects; (6) important social, occupational, or recreational activities are given up or reduced because of substance use; and (7) the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem.

Substance abuse is a pattern of substance use leading to many adverse results from continual use. According to DSM-IV-TR,[10] substance abuse involves one (or more) of the following within a 12-month period: (1) recurrent use resulting in a failure to fulfill major obligations at work, school, or home; (2) recurrent use in situations which are physically hazardous (e.g., driving while intoxicated); (3) legal problems resulting from recurrent use; or (4) continued use despite significant social or interpersonal problems caused by the substance use.

Tourette's Syndrome. Tourette's disorder refers to the condition of multiple motor and vocal tics, which are rapid, recurrent, stereotyped movements. Tics of Tourette's include eye blinking, facial grimacing, throat clearing, grunting, and, uncommonly, although most notably, coprolalia, the uttering of obscenities. The tics typically start around age six (the diagnosis requires that tics must appear by age 18). Pharmacologic treatments that have been tried include antipsychotic medications and medications from other classes, including clonidine, some of the tricyclic antidepressants, and benzodiazepines.

Scope and Key Questions

The Key Questions

Key Question I: What are the leading off-label uses of atypical antipsychotics in the literature? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Question II: What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications, such as depression?

Sub-Key Question II: How do atypical antipsychotic medications compare with other drugs, including consentional antipsychotics, for treating off-label indications?

Key Question III: What subset of the population would potentially benefit from off-label uses? Do efficacy, effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Demographic subsets include different racial/ethnic groups, different age groups, and both genders. For clinical subsets, it is expected that only a small number of trials investigate specific subtypes (for example, inattentive vs hyperactive-impulsive type ADHD) which makes a comparative study infeasible. When data are available, clinical subtypes of the conditions of interest will be examined (for instance, combat-related PTSD and non combat-related PTSD). Severity subsets of population are categorized as groups with mild, moderate, or severe condition.

Key Question IV: What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Question V: What is the effective dose and time limit for off-label indications?

Scope

Study populations covered by the present review are adults, defined as being 18 years old and older, with the following disorders: obsessive-compulsive disorder (OCD), post-traumatic stress disorder (PTSD), personality disorders (primarily borderline), agitation in dementia (primarily in the elderly), anxiety, and major depressive disorder. The following disorders are also studied among children (below 12 years old) and adolescents (12 to 17 years old): eating disorders (including anorexia nervosa and bulimia), attention deficit hyperactivity disorder (ADHD), Tourette's syndrome, and insomnia.

Interventions are the following atypical antipsychotics approved by the U.S. FDA: aripiprazole, olanzapine, quetiapine, risperidone, ziprasidone, paliperidone, asenapine, and iloperidone.

Four types of trials will be classified and examined:

1) "head-to-head" trials: trials that compare one atypical antipsychotic to another and provide direct evidence of comparative efficacy;

2) "active" controlled trials: trials that compare an atypical antipsychotic with another class of medication, often conventional antipsychotics;

3) "placebo" controlled trials: trials that compare atypical antipsychotics with a placebo; and

4) "augmentation" trials: trials that compare an antipsychotic taken with another medication with the other medication alone.

It is possible for a trial to include comparisons of more than one type; for example, a trial comparing risperidone, olanzapine, haloperidol, and placebo would include head-to-head, active, and placebo comparisons.

We will report efficacy and where available, effectiveness outcomes. For efficacy, we will report commonly used objective outcomes such as symptom scores, response rates, laboratory data, and time to disease recurrence; where effectiveness studies are available, we will report these outcomes plus general health outcomes (e.g., SF36) and quality of life.

All reported side effects and adverse events will be abstracted from clinical trials and large observational studies, regardless of study duration. The primary focus will be on the following adverse events: mortality, cardiovascular events (myocardial infarction, arrhythmia – tachycardia, and blood pressure increase / decrease), neurological events (cerebrovascular accident – CVA, akathisia, extrapyramidal symptoms, tardive dyskinesia, sedation, and dizziness), and metabolic disorders (weight gain / loss, hyperglycemia / diabetes, and hyperlipidemia).

Chapter 2. Methods

Topic Development

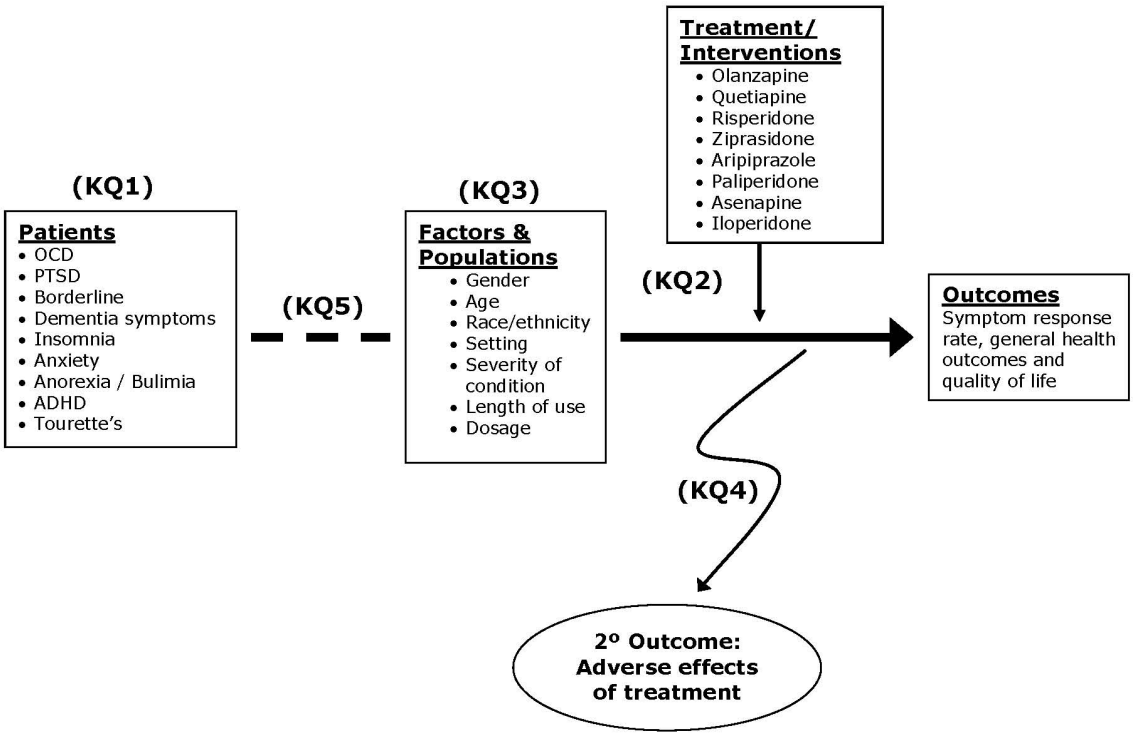
The current report is designed to update "Efficacy and Comparative Effectiveness of Atypical Antipsychotics for Off-label use" report published by AHRQ in 2006. Since this is an update review, we tried to be as consistent as we could with regard to the general topics, scope of work, and analytical methods when possible and appropriate, but made revisions to reflect the important changes mentioned in the introduction. The key questions were posted on the AHRQ Effective Health Care website to obtain public comments which were considered when focusing the scope of this report. The present evidence report focuses on eight FDA-approved atypical antipsychotics (clozapine was excluded because of its documented severe or life-threatening side effects) used for the following psychiatric conditions: anxiety, ADHD, dementia and severe geriatric agitation, depression, eating disorder, insomnia, OCD, PTSD, personality disorders, substance abuse, and Tourette's syndrome. We reviewed all conditions among adults (defined as 18 years old and older); for ADHD, eating disorders, insomnia, and Tourette's syndrome, children (below 12 years old) and adolescents (12 – 17 years old) were also included. Autism, which was included in the original study, is included in a report on the comparative effectiveness of typical and atypical antipsychotics for on-label indications conducted by another EPC. Thus, autism is excluded from the present review.

Analytic Framework

Figure 1 presents the analytic framework for the update of this Comparative Effectiveness Review, with the five key questions depicted. First, by reviewing utilization data, surveys on prescribing patterns, and general information about the leading off-label uses, new off-label uses and trends in utilization in the target populations are summarized. Next, by using data from clinical trials and large cohort studies, evidence of benefits and harms in treating the mental health conditions is documented. The evidence of benefits – efficacy and comparative effectiveness (versus placebo, versus other atypicals, or versus conventional therapy) for the off-label indications – is evaluated separately for each of the atypical antipsychotics within condition (dementia, OCD, PTSD, depression, etc.) via the examination of selected outcome measures, mainly symptom response rates measured by recognized psychometric tools.

Benefits and harms for specific subpopulations (by gender, age, and race/ethnicity) or related to other important factors (setting, severity of condition, length of use, and dosage) are documented. Special attention is given to identify the efficacious dose and time limit for off-label indications. The evidence of risks – adverse events associated with off-label indications – is summarized, firstly within individual drugs across condition, and then compared within the class and with other drugs used for the conditions.

Figure 1. Analytic Framework for Comparative Effectiveness Review: Off-label Uses of Atypical Antipsychotics



Search Strategy

We conducted an initial update search on June 1, 2008 as part of a project to determine if Comparative Effectiveness Reviews (CERs) funded by AHRQ needed updating; this search included only the drugs aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Regular update searches continued through June 2010. The search for off-label use of the newly approved atypicals (iloperidone, paliperidone and asenapine) included all years available in the electronic databases through June 2010. Searches for utilization data were conducted, as were searches for use for new conditions (anxiety, ADHD, eating disorders, insomnia, and substance abuse). Databases searched include: DARE (Database of Abstracts of Reviews of Effects), Cochrane library of systematic reviews, CENTRAL (Cochrane Central Register of Controlled Trials), PubMed (National Library of Medicine, includes MEDLINE), EMBASE (Biomedical and pharmacological bibliographic database), CINAHL (Cumulative Index to Nursing and Allied

Health Literature), and PsycINFO. A summary of detailed search strategies is available in Appendix A. Other sources of literature include clinicaltrials.gov, references of included studies, references of relevant reviews, and personal files from related topic projects. In addition, AHRQ Effective Healthcare Program Scientific Resource Center (SRC) at Oregon Health Sciences University (OHSU) requested unpublished studies from pharmaceutical manufacturers.

Technical Expert Panel

A Technical Expert Panel (TEP) provided expertise and different perspectives on the topic of this review. We invited a distinguished group of scientists and clinicians to participate in the TEP. We aimed to have at least one expert on each psychiatric condition on our TEP. TEP conference calls were held in November 2009 and February 2010. TEP members and their affiliations are listed in the front matter.

The TEP provided valuable information throughout the entire study. It provided information to identify literature search strategies; helped to decide appropriate outcome measures for specific psychiatric conditions and to identify recently published or ongoing clinical trials; and recommended approaches to specific issues raised from the public posting

Study Selection

Two trained researchers reviewed the list of titles resulting from our electronic searches and selected articles to obtain. Each article retrieved was reviewed with a brief screening form (see Appendix B: screener) that collected data on medication, psychiatric condition, study design, population, sample size, and study duration. Only studies on humans were included. Studies that did not report any outcomes of efficacy, effectiveness, safety/adverse events, or utilization patterns were excluded. As single dose or short term trials (less than six weeks in length) are common for several of the new uses, we decided, at the TEP's suggestion, not to limit inclusion by study duration. Clinical trials were used to review efficacy outcomes. In the case that no clinical trials were found for a given condition or drug of interest, we turned to observational studies.

All reported side effects and adverse events were abstracted from clinical trials, even if the trial did not report efficacy or effectiveness results. Reports of utilization and prescribing patterns were accepted if they discussed use in the United States since 1995.

Data Extraction

Data were independently abstracted by a health services researcher and a psychiatrist trained in the critical assessment of evidence. The following data were abstracted from included trials: trial name, setting, population characteristics (including sex, age, ethnicity, and diagnosis), eligibility and exclusion criteria, interventions (dose, frequency, and duration), any co-interventions, other allowed medication, comparisons, and results for each outcome. Data abstraction forms are provided in Appendix B: short form screener and detailed abstraction form.

For efficacy and effectiveness outcomes, a statistician extracted data. Published summary data for each treatment or placebo arm within a trial was collected. For outcomes that reported count data, event counts and sample sizes by group were extracted. For continuous outcomes, sample size, mean difference and standard deviations were extracted. If a study did not report a mean difference by outcome or if a mean difference could not be calculated from the given data, the study was excluded from analysis. For those trials that did not report a follow-up standard deviation, we imputed one by assigning the weighted mean standard deviation from other trials that reported the standard deviation for the same outcome.

Data from publications reporting adverse events were extracted by two reviewers and reconciled by a third. Since the most common type of data reported across adverse event publications were sample size and number of people with each event, we collected this information by treatment. Each event was counted as if it represented a unique individual. Because a single individual might have experienced more than one event, this assumption may have overestimated the number of people having an adverse event. If a trial mentioned a particular type of adverse event in the discussion but did not report data on that adverse event, we did not include that trial in that particular event's analysis. In other words, we did not assume an adverse event occurred unless the trial report specifically stated that some number of events was observed. (By taking this approach, we may have underestimated the number of patients for whom a particular adverse event was observed.) Taking the opposite tack, namely assuming a particular adverse event did not occur in any study if it was not mentioned, certainly underestimates the number of patients for whom a particular adverse event occurred.

Quality Assessment

To assess internal validity, we abstracted data on the adequacy of the randomization method; the adequacy of allocation concealment; maintenance of blinding; similarity of compared groups at baseline and the author's explanation of the effect of any between-group differences in important confounders or prognostic characteristics; specification of eligibility criteria; maintenance of comparable groups (i.e., reporting of dropouts, attrition, crossover, adherence, and contamination); the overall proportion of subjects lost to follow-up and important differences between treatments; use of intent-to-treat analysis; post-randomization exclusions, and source of funding. We defined loss to follow-up as the number of patients excluded from efficacy analyses, expressed as a proportion of the number of patients randomized.

To assess external validity, we recorded the number screened, eligible, and enrolled; the use of run-in and washout periods or highly selective criteria; the use of standard care in the control group; and overall relevance. Funding source was also abstracted.

To arrive at a quantitative measure, we used the Jadad scale, which was developed for drug trials. This method measures quality on a scale that ranges from 0-5, assigning points for randomization, blinding, and accounting for withdrawals and dropouts.[19] Across a broad array of meta-analyses, an evaluation found that trials scoring 0-2 report exaggerated results compared with trials scoring 3-5.[20] The latter have been called "good" quality and the former called "poor" quality.

Applicability

People may use "efficacy" and "effectiveness" of an intervention interchangeably, but they have important differences. Comparative Effectiveness Reviews (CERs) assess internal validity and external validity (e.g., applicability or generalizability) of included studies. Internal validity is emphasized in efficacy studies, while applicability is emphasized in effectiveness studies. The efficacy of an intervention measures the extent to which the intervention works under ideal circumstances, and the effectiveness of an intervention measures the extent to which the intervention works under real world conditions.[21] Therefore, designs of effectiveness trials are based on conditions of routine clinical practice, and outcomes of effectiveness trials are more essential for real world clinical decisions.

The fundamental distinction between efficacy and effectiveness studies lies in the populations and control over the intervention(s).[22] Efficacy studies tend to be performed on referred patients and in specialty settings, and enrolled populations are highly selected (patients with comorbidities may be excluded); effectiveness studies are usually conducted on populations in primary care settings, which reflect the heterogeneity of the general population and thus are more representative. The vast majority of studies included in our report are efficacy studies as there are few effectiveness studies reporting health outcomes of interest. However, effectiveness studies are included in our analyses of adverse events.

Rating the Body of Evidence

We assessed the overall strength of evidence for intervention efficacy using guidance suggested by the U.S. Agency for Healthcare Research and Quality (AHRQ) for its Efffective Healthcare Program.[23] This method is based loosely on one developed by the Grade Working Group,[24] and classifies the grade of evidence according to the following criteria:

> **High** = High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence on 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.

The evidence grade is based on four primary domains (required) and four optional domains. The required domains are risk of bias, consistency, directness, and precision; the additional domains are dose-response, plausible confounders that would decrease the observed effect, strength of association, and publication bias. A brief description of the required domains is displayed in Table 4 below. For this report, we used both this scoring scheme and the global implicit judgment about "confidence" in the result. Where the two disagreed, we went with the lower classification.

Table 4. Grading the strength of a body of evidence: Required domains and their definitions

Domain	Definition and Elements	Score and Application
Risk of Bias	Risk of bias is the degree to which the included studies for a given outcome or comparison have a high likelihood of adequate protection against bias (i.e., good internal validity), assessed through two main elements: • Study design (e.g., RCTs or observational studies) • Aggregate quality of the studies under consideration. Information for this determination comes from the rating of quality (good/fair/poor) done for individual studies	Use one of three levels of aggregate risk of bias: • Low risk of bias • Medium risk of bias • High risk of bias
Consistency	The principal definition of consistency is the degree to which reported effect sizes from included studies appear to have the same direction of effect. This can be assessed through two main elements: • Effect sizes have the same sign (that is, are on the same side of "no effect") • The range of effect sizes is narrow.	Use one of three levels of consistency: • Consistent (i.e., no inconsistency) • Inconsistent • Unknown or not applicable (e.g., single study) As noted in the text, single-study evidence bases (even mega-trials) cannot be judged with respect to consistency. In that instance, use "Consistency unknown (single study)."

Domain	Definition and Elements	Score and Application
Directness	The rating of directness relates to whether the evidence links the interventions directly to health outcomes. For a comparison of two treatments, directness implies that head-to-head trials measure the most important health or ultimate outcomes. Two types of directness, which can coexist , may be of concern: Evidence is indirect if: • It uses intermediate or surrogate outcomes instead of health outcomes. In this case, one body of evidence links the intervention to intermediate outcomes and another body of evidence links the intermediate to most important (health or ultimate) outcomes. • It uses two or more bodies of evidence to compare interventions A and B -- e.g., studies of A vs. placebo and B vs. placebo, or studies of A vs. C and B vs. C but not A vs. B. Indirectness always implies that more than one body of evidence is required to link interventions to the most important health outcomes. Directness may be contingent on the outcomes of interest. EPC authors are expected to make clear the outcomes involved when assessing this domain.	Score dichotomously as one of two levels directness • Direct • Indirect If indirect, specify which of the two types of indirectness account for the rating (or both, if that is the case) -- namely, use of intermediate/ surrogate outcomes rather than health outcomes, and use of indirect comparisons. Comment on the potential weaknesses caused by, or inherent in, the indirect analysis. The EPC should note if both direct and indirect evidence was available, particularly when indirect evidence supports a small body of direct evidence.
Precision	Precision is the degree of certainty surrounding an effect estimate with respect to a given outcome (i.e., for each outcome separately) If a meta-analysis was performed, this will be the confidence interval around the summary effect size.	Score dichotomously as one of two levels of precision: • **Precise** • **Imprecise** A precise estimate is an estimate that would allow a clinically useful conclusion. An imprecise estimate is one for which the confidence interval is wide enough to include clinically distinct conclusions. For example, results may be statistically compatible with both clinically important superiority and inferiority (i.e., the direction of effect is unknown), a circumstance that will preclude a valid conclusion.

Data Synthesis

We constructed evidence tables displaying the study characteristics and results for all included trials (Appendix D). Trials that evaluated one atypical antipsychotic against another and provided direct evidence were classified as "head-to-head" trials. "Active" controlled trials compared an atypical antipsychotic with another class of medication. Trials that compared atypical antipsychotics with a placebo were referred to as "Placebo" controlled trials. Finally, trials that compared an antipsychotic taken with another medication with the other medication alone were examined (referred to as augmentation trials). We provided four separate evidence tables, one for each type of study (head-to-head, active control, placebo control, and augmentation).

Efficacy

For the efficacy analyses, we focused on controlled trials. Effect sizes were calculated for each comparison, for studies reporting a continuous outcome. If all trials within a condition and subgroup used the same scale, then the effect size did not need to be standardized and a mean difference was calculated. For subgroups where pooling was done across several scales, we calculated a standardized mean difference (SMD) using the Hedges' g effect size.[25] A positive effect size indicates that the atypical drug has a higher efficacy than does the comparison arm (active control or placebo arm).

For outcomes that reported count data (number of events), relative risks (RR) were calculated. A RR greater than one indicates that the atypical has higher efficacy than does the comparison arm.

Based on important outcomes suggested by the TEP, a psychiatrist chose which outcomes were most appropriate to pool. Poolability across studies was also important; the psychiatrist, the statistician, and the project team jointly made the selection based on their professional knowledge and also considering the frequency of an outcome measure being reported by the trials. A minimum of three studies was required for meta-analysis. An effect-size or relative risk was calculated for studies that reported data but did not contribute to a pooled analysis.

For trials that were judged sufficiently clinically similar to warrant meta-analysis, we estimated a pooled random-effects estimate[26] of the overall effect size or RR in outcome measures. The individual trial outcomes were weighted by both within-study variation and between-study variation in this synthesis.

We assessed publication bias for each condition that is pooled. Tests were conducted using the Begg adjusted rank correlation test[27] and the Egger regression asymmetry test.[28] Heterogeneity was assessed using the Q test and I-squared[29] test. All meta-analyses were conducted with Stata statistical software, version 10.0 (Stata Corp., College Station, Texas)[30].

We reviewed and when appropriate included studies used in the 2006 Comparative Effectiveness Review (CER). For efficacy outcomes, pooled analysis included both new studies and those included in the 2006 CER when clinically similar.

Adverse Events

All adverse event data from the prior report was combined with adverse event data extracted from new studies, as long as there was no overlap. We identified mutually exclusive groups of similar events, based on clinical expertise. For example, events that affected the head, ear, eye, nose, or throat were grouped together as HEENT. For each adverse-event group, we report the number of trials that provided data for any event in the subgroup. We also report the total number of individuals in the treatment group as well as the number who were observed to have experienced the event. We then report the analogous counts for the control groups.

Adverse events were analyzed based on three comparison types: atypical antipsychotic vs placebo; atypical antypsychotics vs other atypical antipsychotics, and atypical antipsychotics vs another active drug.

For reporting the data on adverse events, we treated each atypical antipsychotic separately and (in general) did not group them together as a class. However, we did summarize the findings of other published analyses that treated these drugs as a class. For our own analyses, we divided the study populations into three groups to make them more clinically homogeneous with respect to adverse events: children and adolescents, adults, and the elderly (i.e. the dementia trials).

For subgroups of events that occurred in two or more trials, we performed a meta-analysis to estimate the pooled odds ratio and its associated 95 percent confidence interval. Given that many of the events were rare, we used exact conditional inference to perform the pooling rather than applying the usual asymptotic methods that assume normality. Asymptotic methods require corrections if zero events are observed; generally, half an event is added to all cells in the outcome-by-treatment (two-by-two) table in order to allow estimation, because these methods are based on assuming continuity. Such corrections can have a major impact on the results when the outcome event is rare. Exact methods do not require such corrections. We conducted the meta-analyses using the statistical software package StatXact Procs v6.1 (Cytel Software, Cambridge, MA).

Any significant pooled odds ratio greater than one indicates the odds of the adverse event associated with the atypical antipsychotic is larger than the odds associated with the comparison (placebo, active control, or other antipsychotic) group. We calculated Number Needed to Harm (NNH) where this occurred. We note that if no events were observed in the comparison group, but events were observed in the intervention group, the odds ratio is infinity and the associated confidence interval is bounded only from below. In such a case, we report the lower bound of the confidence interval. If no events were observed in either group, the odds ratio is undefined, which we denote as “Not calculated (NC)” in the results tables.

Peer Review and Public Commentary

Experts on the various psychiatric conditions as well as various stakeholder and user communities (to be listed in Appendix F of final report) performed an external peer review on this CER. The AHRQ Effective Healthcare Program Scientific Resource Center (SRC) located at Oregon Health Sciences University (OHSU) oversaw the peer review process. Peer reviewers were charged with commenting on the content, structure, and format of the evidence report and encouraged to suggest any relevant studies we may have missed. We compiled all comments and addressed each one individually, revising the text as appropriate. AHRQ and the SRC also requested review from its own staff. The SRC placed the draft report on the AHRQ website (http://effectivehealthcare.ahrq.gov/) for public comment and compiled the comments for our review. We also requested review from each member of our Technical Expert Panel (TEP).

Chapter 3. Results

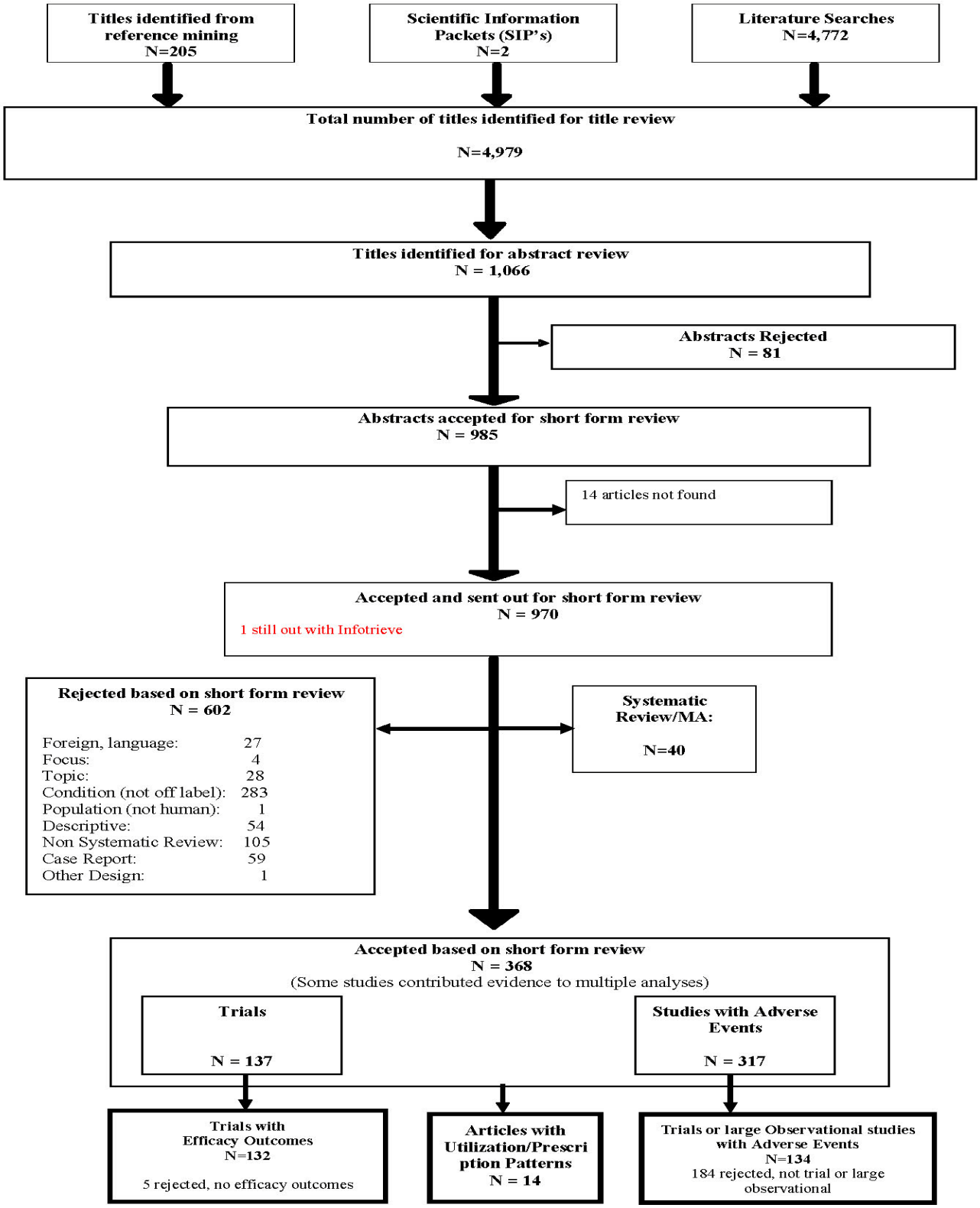
In total, EPC reviewers selected 1,066 relevant titles for abstract review out of 4,979 titles. 4,772 titles were identified from electronic literature searches, 205 were identified from reference mining, and two others not found in the electronic searches were included in Scientific Information Packets (SIPs) sent by drug manufacturers (Figure 2). Eighty-one were rejected through our abstract review, 14 could not be found, and one is still in the process of being retrieved by a contractor (Infotrieve). Thus, 970 full-text articles/ reports were available for short form screening.

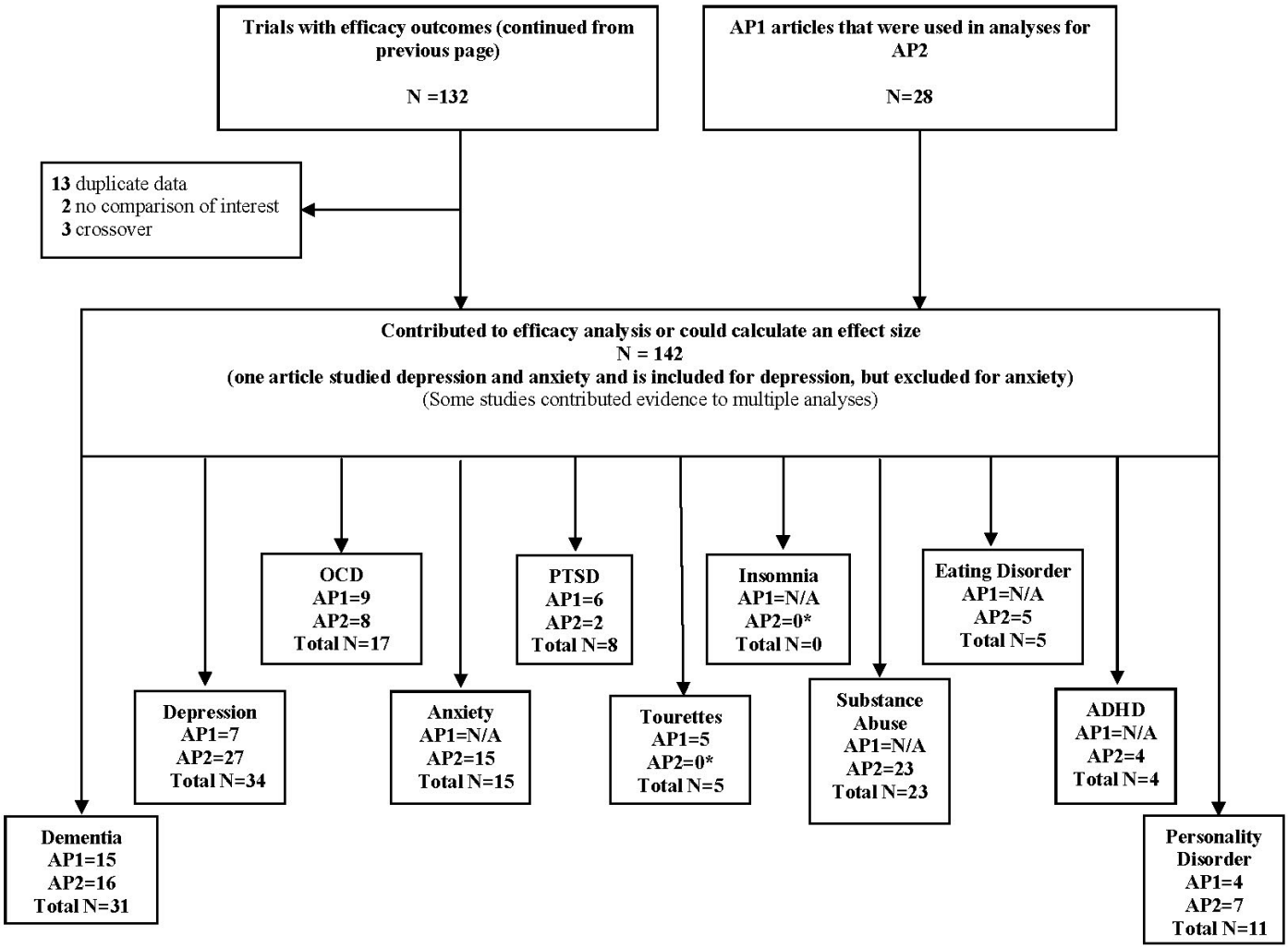
Screening of retrieved articles resulted in further exclusion of 602. Reasons for exclusion include: no psychiatric condition of interest (i.e., not off-label conditions: 283 articles), study design (105 non-systematic reviews, 40 systematic reviews/meta-analysis, 59 case reports, 54 descriptive studies, and one other design), no drug/topic of interest (28 articles), foreign language (27 articles), no efficacy, effectiveness, safety, or utilization outcomes (four articles), and no human cases included (one article).

Among the 368 articles accepted based on short form review, there are 137 controlled trials (of which 132 reported efficacy outcomes) and 317 studies reporting adverse events (in our adverse event analysis, we focused on 133 studies which were either controlled trials or large observational studies). Fourteen articles contain information on utilization/prescription patterns in the U.S.

The second page of Figure 2 displays the breakdown of the 132 new controlled trials that reported efficacy results. Among these trials, 13 reported duplicate data, two had no comparison of interest and three were cross-over studies; all were excluded. We included 28 trials from our 2006 CER, this left us 142 studies in total for our efficacy synthesis, with some studies contributing evidence to multiple conditions. The bottom of the second page of Figure 2 displays detailed numbers of studies by individual condition.

Figure 2. Literature Flow





* Where trials did not exist, we described observational studies.

AP1=Evidence Report 2006, AP2=Updated 2010 Evidence Report

Key Question I.

What are the leading off-label uses of atypical antipsychotics in the literature? How have trends in utilization changed in recent years, including inpatient versus outpatient use? What new uses are being studied in trials?

Key Points

Off-label use of atypical antipsychotics in various settings has increased rapidly since their introduction in the 1990s.

Use of atypical antipsychotics for the following conditions has been documented in the scientific literature: ADHD, anxiety, dementia in elderly patients, depression, eating disorders, insomnia, obsessive compulsive disorder, personality disorder, PTSD, substance use disorders, and Tourette's syndrome.

Risperidone, quetiapine, and olanzapine are the most common atypicals prescribed for off-label use.

There is little reported off-label use of asenapine, iloperidone, and paliperidone.

According to a 2007 study, the use of atypical antipsychotics in the elderly is much higher in long-term care settings than in the community.

In 2004, nearly 25% of the elderly nursing home population received antipsychotics, with most receiving atypicals; males were more likely than females to receive them.

One year after the 2005 FDA advisory warning, no state had actually changed its prior authorization policy in response to limit the use of atypicals in dementia. However, a more recent study concluded that the FDA advisory decreased the use of atypical antipsychotics in the U.S., especially among elderly dementia patients.

In 2003–2004 antipsychotics were only prescribed in 1% of overall mental health visits by children and adolescents, with most (99%) of these visits involving prescribing of atypicals.

At one large acute-care psychiatric hospital, quetiapine was used extensively for off-label conditions, and in a variety of off-label doses: only a quarter of patients had one of the diagnoses for which quetiapine is approved, and only a third received quetiapine in a standing dose

regimen. Depression and substance use disorders were found to be the most common associated diagnoses.

Detailed Analysis

Overall utilization/prescription patterns in the U.S. Our search identified thirty-two papers describing utilization/prescription patterns of antipsychotics (including atypical antipsychotics) in the Unites States. The majority examined typical antipsychotics, atypical antipsychotics, and other agents, simultaneously. Many of them investigated both on-label and off-label uses of atypicals. Considering this, there are actually very few studies documenting patterns of off-label use of atypical antipsychotics specifically. Table 5 presents information about settings, dates, sample size, drugs, conditions, and findings from large U.S. utilization studies with representative populations.

Reports have shown widespread off-label use of atypical antipsychotics in various settings since their introduction in the 1990s,[31-36] and such use has increased significantly in the past decade. The following conditions related to off-label use of atypical antipsychotics have been documented: ADHD, autism, anxiety, dementia, depression, eating disorders, insomnia, obsessive compulsive disorder, personality disorder, PTSD, substance use disorders, and Tourette's syndrome. Three drugs, namely risperidone, quetiapine, and olanzapine, have been identified as the most commonly prescribed agents.

Utilization/prescription patterns among the elderly. Compared to other populations, use of atypical antipsychotics among elderly people has been given more attention, probably due to the increasing use of these drugs in dementia and Alzheimer's[37] and the increasing fatal risk reported with this use. Studies have examined utilization patterns in both long-term care and in community settings in the U.S.

Prescription of atypicals to treat dementia differs by gender and setting. One study[38] found that use of atypical antipsychotics – especially risperidone, olanzapine, and quetiapine – was much higher in long-term care settings (21.0%, 11.9%, and 7.1%, respectively) than in the community (5.1%, 4.0%, and 2.3%, respectively). Another study[39] used the 2004 National Nursing Home Survey data and found widespread off-label use of antipsychotic drugs in conditions such as dementia, anxiety, and depression. Nearly 25% of the elderly nursing home population received antipsychotics, with most receiving atypicals. They also found that males were more likely than females to receive atypicals. However, data from another nationally representative survey,[40] concluded that among community-dwelling elderly, gender was not significantly associated with atypical antipsychotics use. The authors also found significantly increasing use of atypicals among this population: after 1998, atypical use was over ten times more than in 1996 – 1998. Elderly patients with poorer perceived mental health were more likely to receive atypicals rather than typicals. This is consistent with earlier findings.[39]

When increasing evidence showed serious adverse events associated with the use of atypical antipsychotics among elderly people with dementia, regulatory warnings were issued. In both the U.S. and Canada, regulatory agencies (FDA and Health Canada) issued advisory warnings to

health care professionals in 2005, describing increased mortality among elderly people with dementia who were taking atypical antipsychotics. Three studies examined the impact of these warnings. In the U.S., Polinski[41] found that more than one year after the FDA advisory warning, no state had actually changed its prior authorization policy in response to limit the use of atypicals in dementia. A more recent study [42] compared atypical antipsychotics use before and after the FDA advisory and concluded that the FDA advisory was associated with decreases in both on-label and off-label uses of atypical antipsychotics. The decrease was more rapid among elderly patients with dementia. In Canada, Valiyeva[43] found that regulatory warnings were associated with small relative decrease (3% - 5%) in the use of atypicals among elderly patients with dementia, but they did not reduce the overall prescription rate. Despite these decreases, atypical antipsychotics continued to be a common treatment option used among elderly dementia patients.

Utilization/prescription patterns among children and adolescents. A few studies examined prescription patterns of atypical antipsychotics among children and adolescents, indicating wide prescription and recent growth in the treatment of depression, anxiety, and other mental health problems, even though very limited data supporting efficacy of such use exists. The studies mostly discussed utilization in general, without focusing on off-label conditions.

Olfson[44] examined national trends in the outpatient treatment of children and adolescents with antipsychotics from 1993 to 2002. Although not focusing on off-label uses of the drugs, they found that atypical antipsychotics were being widely prescribed to children and adolescents: a sharp increase was found from 2000 to 2002, composing 92.3% of the antipsychotics prescribed in office-based practice. Aparasu[45] found that atypical antipsychotics were extensively prescribed to children and adolescents in 2003 – 2004: in total, antipsychotics were prescribed in 1% of overall visits by children and adolescents, with most (99%) of these visits involving prescribing of atypicals. The most frequently used atypicals were risperidone, quetiapine, and aripiprazole; males and whites were more likely to use these drugs. Finally, Cooper[46] conducted a cohort study to identify new use of antipsychotics among patients aged 2 to 18 years who enrolled in Tennessee's managed care program for Medicaid enrollees and the uninsured (TennCare). They found that new users of antipsychotics nearly doubled from 1996 to 2001; new users of atypicals increased from 6.8% in 1996 to 95.9% in 2001. New use for ADHD increased 2.5-fold, while new use for Tourette's and autism remained stable.

Other relevant utilization findings. Six papers[47-52] examined treatment of PTSD, mostly among Veterans Administration (VA) populations; however, none of them specifically focused on atypical antipsychotics. They documented that antipsychotics (including atypicals) have been frequently used in PTSD and comorbid disorders treatment, while the efficacy of this treatment was generally not evidenced. One study[51] found that atypical antipsychotics were more frequently prescribed when PTSD co-occurred with major depression among a group of Medicaid recipients in New Hampshire.

Philip[53] investigated two-year trends of off-label prescribing practices of quetiapine at an acute-care psychiatric hospital. They found that quetiapine was used extensively for off-label conditions, and in a variety of off-label doses: only a quarter of patients had one of the diagnoses for which quetiapine is approved, and only a third received quetiapine in a standing dose

regimen. Depression and substance use disorders were found to be the most common associated diagnoses.

Antipsychotic monotherapy (use of only one antipsychotic agent), concomitant therapy (simultaneous use of two or more antipsychotic agents), and combination of antipsychotics and other agents have been studied.[33, 35-36, 54] Their findings supported an increasing prevalence of atypical antipsychotics prescription.

Utilization/prescription patterns in other countries. Fifteen papers discuss utilization/prescription patterns of atypical antipsychotics in countries other than the U.S.: five in Canada, two each in France, Australia, and Turkey, and one each in Germany, New Zealand, United Kingdom, and Italy. The studies documented widespread off-label uses of atypical antipsychotics in treating anxiety,[55-59] ADHD,[58, 60] personality disorder,[59] depression,[58-59, 61] dementia,[62-66] and other conditions. Like in the U.S., common off-label use of atypicals and significant increase in such use have been seen in other countries[59, 64, 66-67] risperidone, quetiapine, and olanzapine were the most frequently used atypicals.[56, 58, 64, 66]

Table 5. Large Utilization Studies in the United States

Author / Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
ADULTS								
Dorsey, 2010[42]	Physician Office	2003 - 2008	4,800	Drug prescribing data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole, Paliperidone	Dementia	The FDA Black Box advisory was associated with decrease in the use of atypical antipsychotics (fell 2% overall), especially among the elderly with dementia (fell 19%). Both on-label and off-label uses declined through 2008.
Jano,2008[40]	Community-dwelling	1996 - 2004	32,737	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Anxiety, dementia	The most common diagnoses of antipsychotics use were dementia, anxiety, and schizophrenia; roughly the same proportion received typicals and atypicals; the most frequently used atypicals were risperidone, olanzapine, and quetiapine. After 1998, atypical use was over ten times more than in 1996 – 1998. Elderly patients with poorer perceived mental health were more likely to receive atypicals rather than typicals.
Kamble,2008[39]	Nursing homes	2004	11,939	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Dementia, depression, anxiety	Wide off-label use in conditions such as dementia, anxiety, depression was found among the elderly. Nearly 25% of nursing home elderly received antipsychotics, with most receiving atypicals. Males were more likely than females to receive atypicals.

Author / Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Gruber-Baldini,2007[38]	Nursing homes and community-dwelling	2002	12,697	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone	Dementia, Alzheimer's	Use of atypical antipsychotics, especially olanzapine, quetiapine, and risperidone, was much higher in long-term care settings than in the community.
Morrato,2007[54]	All	1998 - 2003	55,481	Medicaid claim data analysis	Multistate	Olanzapine, Quetiapine, Risperidone	Depression, substance abuse	The mean prevalence of long-term antipsychotic polypharmacy in the year after initiating antipsychotics was 6.4%. Antipsychotic polypharmacy was more common in patients with more severe mental illness.
Sankaranarayanan, 2007[36]	Emergency department (ED)	2000 - 2004	2 million visits	Survey data analysis	Nationally representative	All; not specified	Depression, anxiety, substance use disorder	55% and 8% psychiatric ED visits involved atypical and typical-atypical combination prescriptions, respectively; there were 8-fold and 3.5-fold increase in ED visits with combination and atypical prescriptions, respectively. Patients with depression were more likely to receive atypical versus typical antipsychotics in the ED settings.

Author / Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Sankaranarayanan, 2007[35]	Outpatient	1996 - 2003	356,885	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone	Depression, anxiety, dementia	From 1996/1997 to 2002/2003, visits involving atypical and combination antipsychotics saw large increases: 195% and 149%, respectively, while visits involving typicals decreased by 71%. More atypicals than typicals and combinations were used at US ambulatory care visits by patients with mental health disorders. Atypicals were less likely involved with visits by adults aged 41 to 64 years old and those with public insurance, but more likely by those with depression.
Chen, 2006[68]	All	2001	33,406	Claim data analysis	Georgia	Olanzapine, Quetiapine, Risperidone	All off-label conditions; not specified	The off-label use of antipsychotics is highly prevalent.
Aparasu, 2005[33]	Outpatient	2003 - 2004	2,860	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Depression, anxiety, dementia	Extensive concomitant antipsychotic therapy (simultaneous use of 2 or more antipsychotic agents) was found in outpatient settings. Risperidone, olanzapine, and quetiapine were commonly used in concomitant therapy and monotherapy.

Author / Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Cooper, 2004[46]	All	1996 - 2001	6,803	Cohort study	Tennessee	All; not specified	Tourette's, ADHD	New users of antipsychotics nearly doubled from 1996 to 2001; new users of atypicals increased from 6.8% in 1996 to 95.9% in 2001. New use for ADHD increased 2.5-fold, while new use for Tourette and autism remained stable.
Rosenheck,2001[52]	Department of Veterans Affairs (VA)	1999	73,981	Chart review	Nationally representative	Olanzapine, Quetiapine, Risperidone	Depression, PTSD, Alzheimer's, dementia	Substantial off-label use of atypicals (42.8%) was evidenced, although a majority of patients were diagnosed with schizophrenia.
CHILDREN / ADOLESCENTS								
Aparasu, 2007[45]	Outpatient	2003 - 2004	2.08 million visits	Survey data analysis	Nationally representative	Olanzapine, Quetiapine, Risperidone, Ziprasidone, Aripiprazole	Depression, anxiety	Atypical antipsychotics are being extensively prescribed to children and adolescents: in total, antipsychotics were prescribed in 1% of overall visits by children and adolescents in 2003 - 2004; most (99%) of these visits involved prescribing of atypicals. The most frequently used atypicals were risperidone, quetiapine, and aripiprazole; males and whites were more likely to use these drugs.

Author / Year	Setting	Dates Covered by the Data	Sample Size	How Utilization Assessed	Sample Representative	Drug	Conditions	Findings
Olfson, 2006[44]	Outpatient	1993 - 2002	1,224,000 visits	Survey data analysis	Nationally representative	All; not specified	All; not specify off-label	Atypical antipsychotics are widely prescribed among children and adolescents; a sharply increased use of atypical antipsychotics was found from 2000 to 2002, composing 92.3% of the antipsychotics prescribed in office-based practice.
Patel, 2006[69]	Outpatient	1998 - 2001	7,353	Drug claims review	Texas	All; not specified	Anxiety, depression, ADHD, substance use disorder	Disruptive behavioral disorders, depressive disorders, and bipolar disorders accounted for the top three conditions associated with children and adolescents receiving antipsychotics.

Note: in the table, we excluded five articles which examined mainly adverse events, eight articles which focused on either utilization of other drugs such as typicals/antidepressants or utilization for on-label conditions or both. We did not include articles examining utilization patterns in countries other than the U.S.

Discussion

Most of the utilization studies used national representative survey data or claim data, and their findings reflect national trends. Various settings were covered, including long-term care facilities, communities, inpatient and outpatient settings, Veterans Administration, and emergency department. We found more studies on some drugs (e.g., risperidone, quetiapine, and olanzapine) than others (we found none on recently approved atypicals asenapine, iloperidone, and paliperidone), more studies on some conditions (e.g., dementia, depression, and anxiety) than others (e.g., insomnia, eating disorder, and OCD), and more studies on the elderly than other populations.

The majority of these studies also investigated the utilization/prescription patterns of other drugs (e.g., conventional antipsychotics, antidepressants, other neuroleptics) simultaneously, and many of them did not distinguish on-label and off-label uses. Still, a high prevalence and a rapid increase in off-label use of the atypical agents have been observed, both in the U.S. and internationally. Importantly, a study of over 350,000 records indicated that more atypicals than typicals and combinations were used at U.S. ambulatory care visits[35] by patients with mental health disorders in the period from 1996 to 2003. Some articles pointed out that despite the scarce evidence supporting efficacy of such uses, the atypicals had been widely prescribed among different populations.

Another issue which arose in our review is sociodemographic disparities in off-label prescriptions. Only a handful articles examined prescription patterns by gender and by racial/ethnic group. Although a couple of them found that males and whites were more likely to receive off-label prescription of atypicals, the sparse studies could not lead to a solid conclusion on sociodemographic disparities.

The utilization studies covered mostly from 1996 to 2004; only a few were conducted after the 2005 FDA and Health Canada warnings on possible severe adverse events in the elderly. One recent study indicated that the 2005 regulatory warning was associated with decreases in the overall use of atypical antipsychotics, especially among elderly dementia patients. However, the prevalence of off-label indications of atypical drugs remains high. We conclude that more studies are needed to document the most recent off-label prescription patterns of atypical antipsychotics, especially the newly approved ones, ideally by different sociodemographic populations and by individual off-label indications.

Key Question II.

What does the evidence show regarding the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications, such as depression?

Sub-Key Question 2: How do atypical antipsychotic medications compare with other drugs, including first generation antipsychotics, for treating off-label indications?

Key Points

We found no trials of paliperidone, asenapine, or iloperidone for off-label uses.

Attention deficit – hyperactivity disorder (ADHD). This off-label use was not included in our 2006 evidence report. We found three placebo control trials (PCTs) and one active-control trial for ADHD in children in 2010.

One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale – Parent version (CAS-P) in children with no serious co-occurring disorders.

One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate in mentally retarded children with ADHD.

Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores compared to placebo, in children with bipolar disorder with ADHD.

There were no trials of quetiapine, olanzapine, or ziprasidone for ADHD.

Anxiety. This off-label use was not included in our 2006 evidence report. We found fifteen PCTs of atypicals for this purpose in 2010.

Three trials of quetiapine were clinically similar enough to pool; relative risk of responding on the Hamilton Anxiety Scale (HAM-A) favored the quetiapine group over placebo. There were not enough trials of olanzapine, risperidone, or ziprasidone to pool; these trials had mixed results.

One head-to-head trial showed no difference between risperidone and paroxetine on HAM-A score improvement.

There were no trials of aripiprazole for anxiety disorders.

Dementia. Our 2006 CER focused on two published meta-analyses on use of atypicals in elderly patients with dementia. They found small but statistically significant effects for treatment with risperidone and aripiprazole, and trends toward efficacy of olanzapine and quetiapine.

The number of new trials published since 2006 justified conducting our own new meta-analysis.

In our pooled analysis of overall efficacy, aripiprazole, olanzapine, quetiapine, and risperidone were superior to placebo as measured by total scores on BEHAVE-D, BPRS, and NPI. Aripiprazole (4 PCTs) and risperidone (6 PCTs) were superior to placebo in decreasing psychosis symptoms in elderly patients with dementia. Results for olanzapine (6 PCTs) and quetiapine (3 PCTs) did not meet conventional levels of statistical significance.

In our pooled analysis on agitation outcomes, aripiprazole (3 PCTs), olanzapine (4 PCTs), and risperidone (6 PCTs) were superior to placebo. Results for quetiapine (5 PCTs) did not meet conventional levels of statistical significance.

There were no trials of ziprasidone in dementia patients.

Three head-to-head trials compared atypicals for dementia; none was found superior.

We pooled five head-to-head trials of atypicals versus haloperidol; there was no statistical difference in effect. There were too few trials to pool by specific atypical.

Depression - Major depressive disorder (MDD). Our 2006 CER reported that atypicals were not more effective as augmentation to SSRIs than placebo at 8 weeks. However, in some trials they led to more rapid improvement (2 to 4 weeks).

By 2010, new trials augmenting both SSRIs and SNRIs with atypicals had been conducted and published. We were able to conduct new meta-analyses which showed atypicals have efficacy in treatment of depression when used as augmentation.

In our pooled analysis**,** the relative risk of responding on Hamilton depression (HAM-D) scores for participants taking quetiapine (3 PCTs) or risperidone (3 PCTs) was significantly higher than for those taking placebo. Olanzapine had only two PCTs, so pooling was not performed; results of these trials did show olanzapine superior to placebo.

Other trials reported the Montgomery-Asberg Depression Rating Score (MADRS); the relative risk of responding for participants taking aripiprazole (3 PCTs) or quetiapine (7 PCTs) was significantly higher than for placebo. Risperidone was only included in one PCT that

reported MADRS; the drug was statistically superior to placebo. One PCT of ziprasidone reported MADRS outcomes; results were statistically superior to placebo.

The three olanzapine PCTs (included in our original 2006 report) found the drug inefficacious as monotherapy for MDD. Since then, one trial of quetiapine as monotherapy was published. Quetiapine significantly increased the time to depressed event, compared to placebo.

No head-to-head trials of atypicals for depression were found.

Eating disorders. This off-label use was not included in our 2006 report. Four trials of olanzapine were found; three reporting Body Mass Index (BMI) outcomes could be pooled. There was no difference in BMI increase at one or three months between participants taking olanzapine and those taking placebo.

There were no trials of aripiprazole, quetiapine, risperidone, or ziprasidone for treatment of eating disorders.

Insomnia. This off-label use was not included in our 2006 report. We found no trials of atypicals for this use.

Two observational studies of olanzapine and four of quetiapine found promising improvements in sleep quality and sleep onset.

No observational studies of aripiprazole, risperidone, or ziprasidone for insomnia were found.

Obsessive Compulsive Disorder (OCD). Our 2006 meta-analysis found atypicals had a clinically important benefit when used as augmentation to SSRIs.

Our 2010 analysis of PCTs reporting YBOCS (Yale-Brown Obsessive Compulsive Scale) outcomes showed significant effects for quetiapine (6 PCTs) and risperidone (3 PCTs) as augmentation in treatment refractory patients. There were too few trials (two) to permit separate pooling for olanzapine; difference in effect versus placebo was statistically insignificant in both studies.

No trials of aripiprazole for OCD were found.

One new trial showed quetiapine produced a significant reduction in YBOCS score, while clomipramine did not.

Two new trials found quetiapine superior to placebo as augmentation to citalopram according to YBOCS and CGI-I scores.

One new head-to-head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation for OCD. Another new head-to-head trial found quetiapine had greater efficacy than ziprasidone for this purpose.

Personality Disorders. Our 2006 CER found three trials of olanzapine for borderline personality disorder (BPD); all reported efficacy of the drug.

Since the original CER was published, PCTs using atypicals for treatment of borderline personality disorder (BPD) have shown mixed results. Due to heterogeneity of outcomes, we could not perform a meta-analysis.

Olanzapine had mixed results in seven trials, aripiprazole showed efficacy in two trials, quetiapine had efficacy in one trial, and ziprasidone was found inefficacious in one trial.

Risperidone had mixed results when used to treat schizotypal personality disorder in two small trials.

No head-to-head trials of atypicals for personality disorder were found.

Post traumatic Stress Disorder (PTSD). Our 2006 CER reported on three PCTs of atypicals as augmentation for PTSD in male veterans and three PCTs as monotherapy in abused women. We had insufficient trials to conduct meta-analysis. The trials for combat-related PTSD had beneficial results, while the other trials had mixed results.

In 2010, five PCTs were clinically similar enough to pool using the change in Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone (4 trials) was superior to placebo. The other trial found olanzapine superior to placebo.

In our meta-analysis of risperidone treatment by trial length, pooled results from at least 12 weeks follow-up were not statistically different from those reported at less than 12 weeks.

In our meta-analysis by condition, atypicals showed efficacy in treatment of combat-related PTSD but not PTSD in abused women.

No trials of aripiprazole, quetiapine, or ziprasidone for PTSD were found.

No head-to-head trials of atypicals for PTSD were found.

Substance abuse. This off-label use was not included in our 2006 CER. We found two PCTs of aripiprazole and one of quetiapine that reported the percent of alcohol abusers completely abstinent during follow-up period. In our pooled analysis, the drugs had insignificant efficacy compared to placebo.

We also pooled two PCTs of olanzapine and one of risperidone in cocaine users. There was no difference in efficacy versus placebo as measured by change in Addiction Severity Index (ASI).

One PCT found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another PCT found aripiprazole inefficacious in reducing craving for methamphetamine.

One PCT of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.

One trial of aripiprazole versus naltrexone in alcohol abusers found no difference in either mean number of days abstinent or percentage of participants completely abstinent.

One trial of risperidone versus pergolide found neither more efficacious than placebo in reducing cocaine use.

There were no head-to-head trials of atypicals for substance abuse.

Tourette's syndrome. No new trials of atypicals have been published since our 2006 CER reported that risperidone was superior to placebo in one small PCT, and it was at least as efficacious as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One PCT of ziprasidone showed variable efficacy compared to placebo.

Detailed Analysis

ADHD. This off-label use was not included in our 2006 systematic review. In 2010 we found no prior meta-analyses or systematic reviews on atypical antipsychotics for attention deficit hyperactivity disorder (ADHD). There were four RCTs; two reported on risperidone and two on aripiprazole. The trials lasted either four or six weeks. Sample sizes were small, ranging from 16 to 45 participants. Trial quality was adequate; the mean Jadad score was 3.5. We were unable to conduct a meta-analysis due to heterogeneity of the outcomes. The studies are displayed in Table 6.

One risperidone study showed that 100% of the patients "responded," as defined by improving at least 30% on the Children's Aggression Scale (CAS-P). This compares to 77% of the placebo patients.[70] The other risperidone study[71] compared risperidone to methylphenidate in children and adolescents with both ADHD and moderate mental retardation. Using the Swanson, Nolan, and Pelham rating scale (SNAP-IV), they found reduced ADHD symptoms with both treatments, with a greater reduction of symptoms with risperidone than methylphenidate. They also found adverse effects of weight gain with risperidone, whereas the other risperidone study had found no weight difference from placebo.[71]

The two studies of aripiprazole involved children with both ADHD and bipolar disorder. Neither showed a difference in ADHD symptoms per the SNAP-IV. One study looked at aripirazole vs placebo and listed adverse events of somnolence and sialorrhea.[72] The other compared aripiprazole plus placebo vs aripiprazole plus methylphenidate and included the adverse effect of one patient experiencing a severe bipolar mixed episode while on aripiprazole and methylphenidate.[73]

Table 6. Atypical antipsychotics for ADHD

Study/Type	Treatment	N	Dose/Duration	ADHD-Measures	Effects
Armenteros, 2007[70]/RCT	Risperidone vs Placebo	25	1.08 mg (mean) + psychostimulant/ 4 weeks	CAS-P CAS-T	100% of risperidone patients improved 30% over baseline in CAS-P compared to only 77% of placebo. No change in CAS-T
CorreiaFilho, 2005[71]/RCT	Risperidone vs methylphenidate (ADHD+Mental retardation)	45	2.9 mg (mean)/ 4 weeks	SNAP-IV	Reduced ADHD symptoms in both per SNAP-IV, greater in risperidone than methylphenidate
Tramontina, 2009[72]/RCT	Aripiprazole vs. Placebo (ADHD+Bipolar)	43	6 weeks	SNAP-IV	No difference in ADHD symptoms
Zeni, 2009[73]/RCT	Aripiprazole + methylphenidate or placebo (ADHD+Bipolar)	16	2+2 week crossover	SNAP-IV	No improvement in ADHD symptoms

ANXIETY. Anxiety is also a new clinical topic not included in our 2006 review. We found one prior meta-analysis on use of atypicals for this condition.[74] However, this analysis combined obsessive compulsive disorder (OCD) trials with trials for generalized anxiety disorder (GAD). We choose to conduct separate analyses for these two conditions; the results for OCD are described later in this report.

Our literature search identified 18 reports of trials that evaluated the use of olanzapine,[75-76] quetiapine,[77-80 81-87] risperidone,[88-91] or ziprasidone[92] for the treatment of anxiety. Jadad scores ranged from two to five; mean score was 3.1. Sample sizes varied widely, from seven to 473. Follow-up time ranged from same day (for public speaking anxiety) to one year. Two articles were abstracts describing a trial for which we had the main article;[81-82] only the main trial was considered for further analysis.[80] One trial had no placebo comparison group and thus was not considered for further analysis.[88] This eight week head-to-head trial of risperidone and paroxetine found statistically significant improvements in the Hamilton Anxiety Scale (HAM-A) for both groups and no difference between treatment groups on several other anxiety measures.[88]

Of the remaining 15 PCTs, all but three[75, 83, 87] reported an outcome measure based on the HAM-A. These three trials studied social anxiety or social phobia. The first of these trials found olanzapine superior to placebo in the treatment of social anxiety disorder;[75] the other two studied quetiapine and did not find it superior to placebo.[83, 87]

The remaining 12 PCTs ranged from six to 18 weeks in duration. One augmentation study of quetiapine and SSRI/venlafaxine versus placebo was not considered further for analysis due to heterogeneity.

Six of remaining PCTs assessed quetiapine, three evaluated risperidone or risperidone augmentation,[89-91] one assessed olanzapine[76] and one studied ziprasidone.[92] These trials either reported the mean score on the HAM-A or the percent of participants that responded to treatment as measured by the HAM-A. Since trials did not consistently report the information needed to calculate a weighted mean difference for pooling of the HAM-A total score, we used the number of participants that responded to treatment as the outcome to pool. The trials defined 'responders' as participants who decreased their HAM-A score by at least 50%.

The one ziprasidone PCT[92] and three PCTs of quetiapine[77, 84-85] did not report the percent or count of participants that responded to treatment and thus could not be pooled. The first of these quetiapine trials used the drug as augmentation of paroxetine for the treatment of refractory generalized anxiety disorder. This study did not find a significant benefit for quetiapine over placebo augmentation.[77] The second studied quetiapine in the treatment of anxiety in patients with bipolar depression and found efficacy over placebo when used in those with bipolar type 1.[84] The third studied quetiapine monotherapy for maintenance treatment of generalized anxiety disorder and found a reduced risk of relapse of anxiety events compared to placebo.[85] The ziprasidone PCT[92] reported no difference in HAM-A score at 8 weeks, compared to placebo.

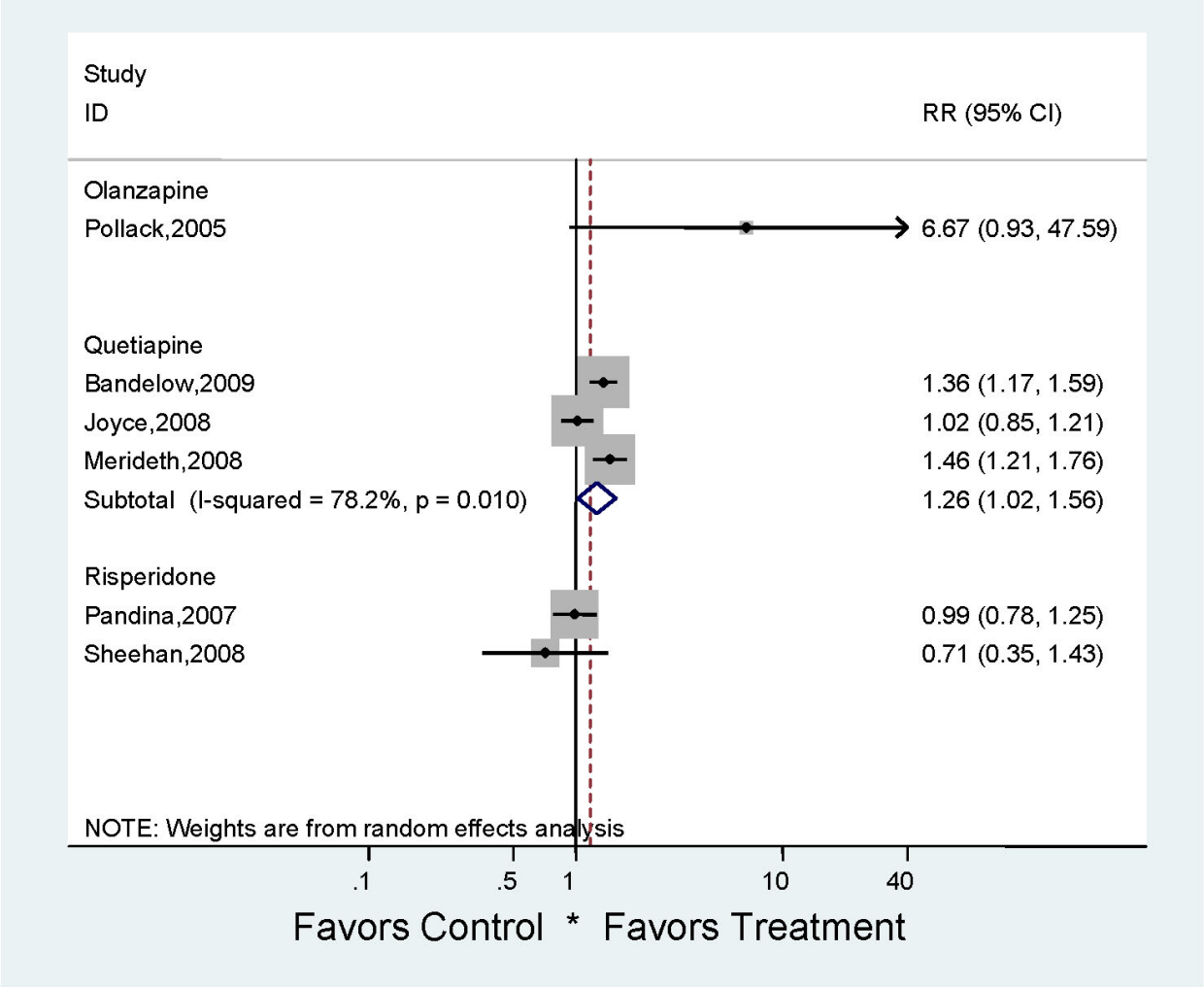
The remaining three trials of quetiapine versus placebo listed in Table 7, were pooled.[79-80, 86] The trials were similar in size ranging from 710 to 873 participants and all had a quetiapine 150mg comparison group that was used in the analysis. The results are displayed in Figure 3, along with the olanzapine and risperidone PCTs. The pooled estimate of the relative risk of responding on the HAM-A was 1.26 (95% CI 1.02, 1.56) in favor of the quetiapine groups. Resulting NNT (Number needed to treat) is eight for one responder as measured by HAM-A. The I-squared statistic was 78.2%, indicating heterogeneity. Neither Begg's nor Egger's test for publication bias indicated the presence of bias (p=1.00, p=0.939, respectively).

Table 7. Generalized Anxiety Disorder – PCTs contributing to analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Pollack et al. 2006[76]	18-72 years old, DSM-IV GAD comorbid depression, dysthymia, and other anxiety disorders except for PTSD and OCD, if GAD was considered primary by the clinician and patient based on disorder severity and associated distress	24	Placebo Olanzapine 2.5-20 mg/day	6 weeks	% Responders on HAM-A: Olanzapine vs Placebo – Relative Risk (RR) = 6.67 (0.93 , 47.59)
Bandelow et al. 2009[80]	18-65 years old, diagnosed GAD, HAM-A total score >= 20 with item 1 and 2 scores >= 2, MADRS total score <= 16, CGI-S score >=4 at enrolment and randomization	873	Placebo Quetiapine 50-150 mg/day Quetiapine 50 mg/day Paroxetine 20 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - Relative Risk (RR) = 1.36 (1.17 , 1.59)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Joyce et al. 2008[86]	Diagnosed GAD	710	Placebo Quetiapine 50 mg/day Quetiapine 150 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - Relative Risk (RR) = 1.02 (0.85 , 1.21)
Merideth et al. 2008[79]	DSM-IV diagnosis of GAD, HAM-A total score >=20 with item 1 and item 2 scores >=2, CGI-S >=4, MADRS <=16	854	Placebo Escitalopram 10 mg/day Quetiapine 150 mg/day Quetiapine 300 mg/day	8 weeks	% Responders on HAM-A: Quetiapine vs Placebo - Relative Risk (RR) = 1.46 (1.21 , 1.76)
Pandina et al. 2007[91]	15-65 years old, diagnosed GAD, CGI-S >=4, antidepressant, benzodiazepine, buspirone or a combination of an antidepressants plus benzodiazepine or buspirone for at least 8 weeks prior and stable x 4 weeks	417	Placebo 0.25-2 mg/day Risperidone 0.25-2 mg/day	4 weeks	% Responders on HAM-A: Risperidone vs Placebo - Relative Risk (RR) = 0.99 (0.78 , 1.25)
Sheehan et al. 2009[89]	18-65, bipolar I, II or NOS and lifetime panic or GAD, CGI-BP<=4, CGI-S>=4	111	Placebo Risperidone 0.5-4 mg/day	8 weeks	% Responders on HAM-A: Risperidone vs Placebo - Relative Risk (RR) = 0.71 (0.35 , 1.43)

Figure 3. Anxiety % Responders on Hamilton Anxiety Scale



DEMENTIA. Our 2006 systematic review reported on two published meta-analyses assessing risperidone, quetiapine, and olanzapine for symptoms of dementia in the elderly,[93-94] and one additional meta-analysis solely on risperidone.[95] In summary, they found small but statistically significant effects for treatment with risperidone and aripiprazole, and trends toward efficacy of olanzapine and quetiapine. Since 2006, one new meta-analysis[96] found no statistically or clinically significant difference between atypicals and placebo. In 2010, we were able to conduct new meta-analyses which included all trials from the previously published analyses plus several newer trials.

We reviewed 31 total trials that reported on dementia. Some were reported in multiple journal articles. Nineteen compared an atypical to placebo: four aripiprazole,[97-99] five olanzapine,[100] &[101-102] five quetiapine,[100, 103-105] and six risperidone.[100-101, 106-107] Seven trials compared an atypical to another active drug.[102, 108-109]&[105, 110-113] Three trials compared one atypical drug to another;[100, 114]&[101] two are also included in our PCT analyses. Two compared the continuation of an atypical to a cessation group.[115-116] One study did not report outcome

data.[117] The quality of the trials varied widely, with Jadad scores ranging from zero to five; mean score was 3.2. Mean sample size was 123; range was 22 to 354. Follow-up times ranged from same day to one year.

Nineteen PCTs reported outcomes between eight and twelve weeks; this range was considered sufficiently clinically similar to pool. These PCTs are described in detail in Table 8. We grouped study outcomes into three categories: total/global scores, psychosis, and agitation. Several PCTs contained more than one treatment arm; these studies compared different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome for each trial. This was most often done for aripiprazole trials that included a 2.5, and 10 mg arm. We present the results by dosage later in the relevant section (Key Question Five).

There was a positive, significant difference between the atypicals as a class and placebo for all three outcome measures: total/global scores (SMD 0.16 (95% CI 0.0.09, 0.23)), psychosis (SMD 0.12 (95% CI 0.05, 0.20)), and agitation (SMD 0.20 (95% CI 0.13, 0.27)). While the minimum clinically important difference is not known, these effect sizes are generally considered "small" in magnitude. For total/global scores, each drug studied (aripriprazole, olanzapine, quetiapine and risperidone) was superior to placebo. The I-squared values indicated minimal heterogeneity (range 27.1% - 35.3%). Results are displayed in Figures 4 to 6.

For treatment of psychosis, while not statistically significant, results favored risperidone and aripiprazole when compared to quetiapine or olanzapine. As measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI, pooled estimates of standardized mean difference (SMD) in effect size were 0.20 (95% CI 0.05, 0.35) for aripiprazole (4 trials) and 0.20 (95% CI 0.08, 0.32) for risperidone (6 trials). Results for olanzapine (6 studies) and quetiapine (3 studies) did not meet conventional levels of statistical significance. Standardized mean difference for olanzapine was 0.05 (95% CI -0.07, 0.17) and for quetiapine -0.03 (95% CI -0.24, 0.18).

To assess effects on agitation, we pooled scores on the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Pooled estimates of standardized mean difference (SMD) in effect size were 0.29 (95% CI 0.16, 0.42) for aripiprazole (3 trials), 0.19 (95% CI 0.07, 0.31) for olanzapine (4 trials), and 0.22 (95% CI 10.09, 0.35) for risperidone (6 trials); once again these trials are generally considered "small" effects. Results for quetiapine (5 studies) did not meet conventional levels of statistical significance: 0.05 (95% CI -0.14, 0.25).

Three head-to-head trials compared atypicals on total/global scores and psychosis outcomes. None was found superior. Results are displayed in Figures 7 to 9.

Finally we conducted a meta-analysis by pooling five trials[102, 105, 108, 112 118] which compared atypicals to haloperidol on total score. Difference between atypicals and haloperidol was not significant. There were too few trials to pool results separately by drug. Regarding psychosis symptoms, we found one trial which showed no difference in efficacy between olanzapine and haloperidol. Results are displayed in Figures 10 and 11.

Table 8. Dementia – PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Breder et al. 2004[119]	Psychosis/psychotic features, Nursing home resident, NPI or NPI/NH >= 6 sum of hallucinations and delusional items, Age 55-95, MMSE = 6-22	487	Placebo Aripiprazole 5 mg/day Aripiprazole 2 mg/day Aripiprazole 10 mg/day	10 weeks	Total/Global Scores: Aripiprazole vs. Placebo-Standardized Mean Difference (SMD)=0.15 (-0.06, 0.36) Psychosis score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= 0.20 (-0.01, 0.41) Agitation score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= 0.27 (0.05, 0.48)
DeDeyn et al. 2003[94]	AD with psychosis	208	Placebo Aripiprazole 2–15 mg/day	10 weeks	Total/Global Scores Aripiprazole vs Placebo - Standardized Mean Difference (SMD) =0.06 (-0.21, 0.34) Psychosis score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= 0.16 (-0.12, 0.43)
Mintzer et al. 2007[97]	Diagnosed with AD and delusions / hallucinations. Institutionalized, capable of self-locomotion, MMSE 6-22. NPI-NH score >=6	487	Placebo Aripiprazole 2 mg/day Aripiprazole 5 mg/day Aripiprazole 5-10 mg/day	10 weeks	Total/Global Scores Aripiprazole vs Placebo - Standardized Mean Difference (SMD) = 0.16 (-0.05 , 0.37) Psychosis score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)=0.24 (0.03, 0.45) Agitation score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= 0.31 (0.10, 0.52)
Streim et al. 2004[120] Streim et al. 2008[98]	AD with psychosis, Age 55-95, MMSE = 6-22, NPI or NPI/NH ≥ 6 sum of hallucinations and delusional items, hallucinations and delusions >=1 month	256	Placebo Aripiprazole 8.6 mg/day	10 weeks	Total/Global Scores Aripiprazole vs Placebo - Standardized Mean Difference (SMD) =0.36 (0.11, 0.61) Psychosis score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= -0.02 (-0.27, 0.23) Agitation score: Aripiprazole vs Placebo-Standardized Mean Difference (SMD)= 0.30 (0.05, 0.55)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
DeDeyn et al. 2004[121]	Age >= 40, Hospitalized/ institutionalized, Psychosis/psychotic features, MMSE = 5-26	NR	Placebo Olanzapine 1.0 mg/day Olanzapine 2.5 mg/day Olanzapine 5.0 mg/day Olanzapine 7.5 mg/day	10 weeks	Total/Global Scores Olanzapine vs Placebo - Standardized Mean Difference (SMD) = 0.14 (-0.05, 0.34) Psychosis score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)= 0.17 (-0.02, 0.37) Agitation score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.14 (-0.05, 0.33)
Deberdt et al. 2004[122]	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items	494	Placebo Olanzapine 5.2 mg Risperidone 1.0 mg	10 weeks	Total/Global Scores Olanzapine vs Placebo - Standardized Mean Difference (SMD) = -0.02(-0.27, 0.23) Total/Global Scores Risperidone vs Placebo - Standardized Mean Difference (SMD) =-0.13 (-0.38, 0.12) Psychosis score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=-0.12 (-0.36, 0.13) Risperidone vs Placebo-Standardized Mean Difference (SMD)=-0.03 (-0.34, 0.16) Agitation score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.09 (-0.16, 0.34) Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.14 (-0.11, 0.39)
Kennedy et al. 2005[123]	Age ≥ 40, MMSE 14-26	268	Placebo Olanzapine 2.5-7.5 mg/day	26 weeks	Psychosis score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=-0.07 (0.33, 0.18)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Schneider, et al. 2006[101] Sultzer et al. 2008[100]	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on (BPRS), ambulatory and living at home or in an assisted-living facility	421	Placebo Olanzapine 5.5mg/day Quetiapine 56.5 mg/day Risperidone 1.0 mg/day	12 weeks	Total/Global Scores Olanzapine vs Placebo - Standardized Mean Difference (SMD) =0.15 (-0.11, 0.40) Quetiapine vs Placebo - Standardized Mean Difference (SMD) = 0.15 (-0.11, 0.40) Risperidone vs Placebo - Standardized Mean Difference (SMD) =0.40 (0.13, 0.68) Psychosis score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.07 (-0.19, 033) Quetiapine vs Placebo-Standardized Mean Difference (SMD)=0.16 (-0.10, 0.42) Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.38 (0.11, 0.66) Agitation score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.28 (0.02, 0.53) Quetiapine vs Placebo-Standardized Mean Difference (SMD)=0.20 (-0.06, 0.46) Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.10 (-0.17, 0.37)
Street et al. 2000[124]	Possible or probable AD, NPI/NH ≥ 3	206	Placebo Olanzapine 5 mg/day Olanzapine 10 mg/day Olanzapine 15 mg/day	6 weeks	Total/Global Scores Olanzapine vs Placebo - Standardized Mean Difference (SMD) = 0.30 (-0.03, 0.63) Psychosis score: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.17 (-0.17, 0.50) Agitation score at 9 weeks: Olanzapine vs Placebo-Standardized Mean Difference (SMD)=0.39 (0.05, 0.72)
Ballard et al. 2005[125]	CMAI >= 39,Age >= 60, NPI >= 4	93	Placebo Rivastigmine min 9 mg/day Quetiapine 100 mg/day	26 weeks	Agitation score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=-0.13 (-0.66, 0.39)
Paleacu et al. 2008[104]	AD with BPSD, age > 50, MMSE < 24, NPI > 6 on any item	40	Placebo Quetiapine 50-300 mg/day	6 weeks	Agitation score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=-0.48 (-1.11, 0.15)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Tariot et al. 2002[94]	Elderly patients with psychosis	378	Placebo Quetiapine 25–600 mg	10 weeks	Total/Global Scores Quetiapine vs Placebo - Standardized Mean Difference (SMD) = 0.22 (-0.03, 0.47) Psychosis score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=0.00 (-0.24, 0.25)
Tariot et al. 2006[105]	Diagnosed with DSM-IV AD, > 64 years old, not bedridden, nursing home residents for >= 2 weeks, presence of psychosis, BPRS scores >=24, CGI-S scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPI-NH, scores of >= 5 on MMSE	284	Placebo Haloperidol 0.5-12 mg/day Quetiapine 25-600 mg/day	10 weeks	Total/Global Scores Quetiapine vs Placebo - Standardized Mean Difference (SMD) =0.00 (-0.29, 0.30) Agitation score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=0.24 (-0.05, 0.54)
Zhong et al. 2004[126] Zhong et al. 2007[103]	Institutionalized, diagnosed possible AD or vascular dementia, age >= 55, ambulatory, agitation that didn't result directly from participants medical condition, PANSS-EC total >= 14, one of the 5 PANSS-EC items >= 4.	333	Placebo Quetiapine 100 mg/day Quetiapine 200 mg/day	10 weeks	Total/Global Scores Quetiapine vs Placebo - Standardized Mean Difference (SMD) =0.04 (-0.21, 0.28) Psychosis score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=-0.03 (-0.27, 0.21) Agitation score: Quetiapine vs Placebo-Standardized Mean Difference (SMD)=-0.03 (-0.27, 0.21)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Brodaty et al. 2003[127] Brodaty et al. 2005[107]	Age >= 55,FAST > = 4,MMSE< = 23, CMAI score of >= 4 on at least 1 aggressive item or a score of 3 on at least 2 aggressive items, or a score of 2 on at least 3 aggressive items, or 2 aggressive items occurring at a frequency of 2 and 1 at a frequency of 3, Nursing home resident, Resident >= 1 month prior to enrollment	345	Placebo 1.06 mg/day Risperidone 0.95 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - Standardized Mean Difference (SMD) = 0.46 (0.23, 0.69) Psychosis score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.36 (0.13, 0.59) Agitation score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.37 (0.14, 0.59)
Dedeyn et al. 1999[118]	Age >= 55, Hospitalized/institutionalized, FAST >= 4, MMSE <= 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD >= 8	344	Placebo Haloperidol 1.2 mg/day Risperidone 1.1 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - Standardized Mean Difference (SMD) =0.12 (-0.14, 0.38) Agitation score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.31 (0.05, 0.57)
Katz et al. 1999[128]	Age >= 55, FAST >= 4, MMSE <= 23, BEHAVE-AD >= 8, BEHAVE-AD global rating >= 1	625	Placebo Risperidone 0.5 mg/day Risperidone 1 mg/day Risperidone 2 mg/day	12 weeks	Total/Global Scores Risperidone vs Placebo - Standardized Mean Difference (SMD) = 0.32 (0.11, 0.53) Psychosis score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.20 (-0.01, 0.41) Agitation score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.38 (0.17, 0.60)
Mintzer et al. 2004[129]	MMSE = 5-23, Age >= 55, BEHAVE-AD Psychosis Subscale >= 2, Able to ambulate, walk with assistance or use wheelchair independently	473	Placebo 53.1 mg Risperidone 1.2 mg	8 weeks	Total/Global Scores Risperidone vs Placebo - Standardized Mean Difference (SMD) =0.17 (-0.11, 0.35) Psychosis score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.17(-0.01, 0.35)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Mintzer et al. 2006[106]	>= 55 years old, residents of nursing homes or long-term care facilities, mobile, met the criteria for psychosis of AD, in need of treatment with an atypical antipsychotic, scored >=2 on any item of the BEHAVE-AD psychosis subscale, MMSE 5-23	473	Placebo Risperidone 0.5-2.5 mg/day	8 weeks	Total/Global Scores: Risperidone vs Placebo - Standardized Mean Difference (SMD) =-0.01 (-0.21, 0.18) Psychosis score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.17 (-0.02, 0.36) Agitation score: Risperidone vs Placebo-Standardized Mean Difference (SMD)=0.04 (-0.16, 0.23)

Figure 4. Dementia Placebo Comparisons – Total/ Global Scores

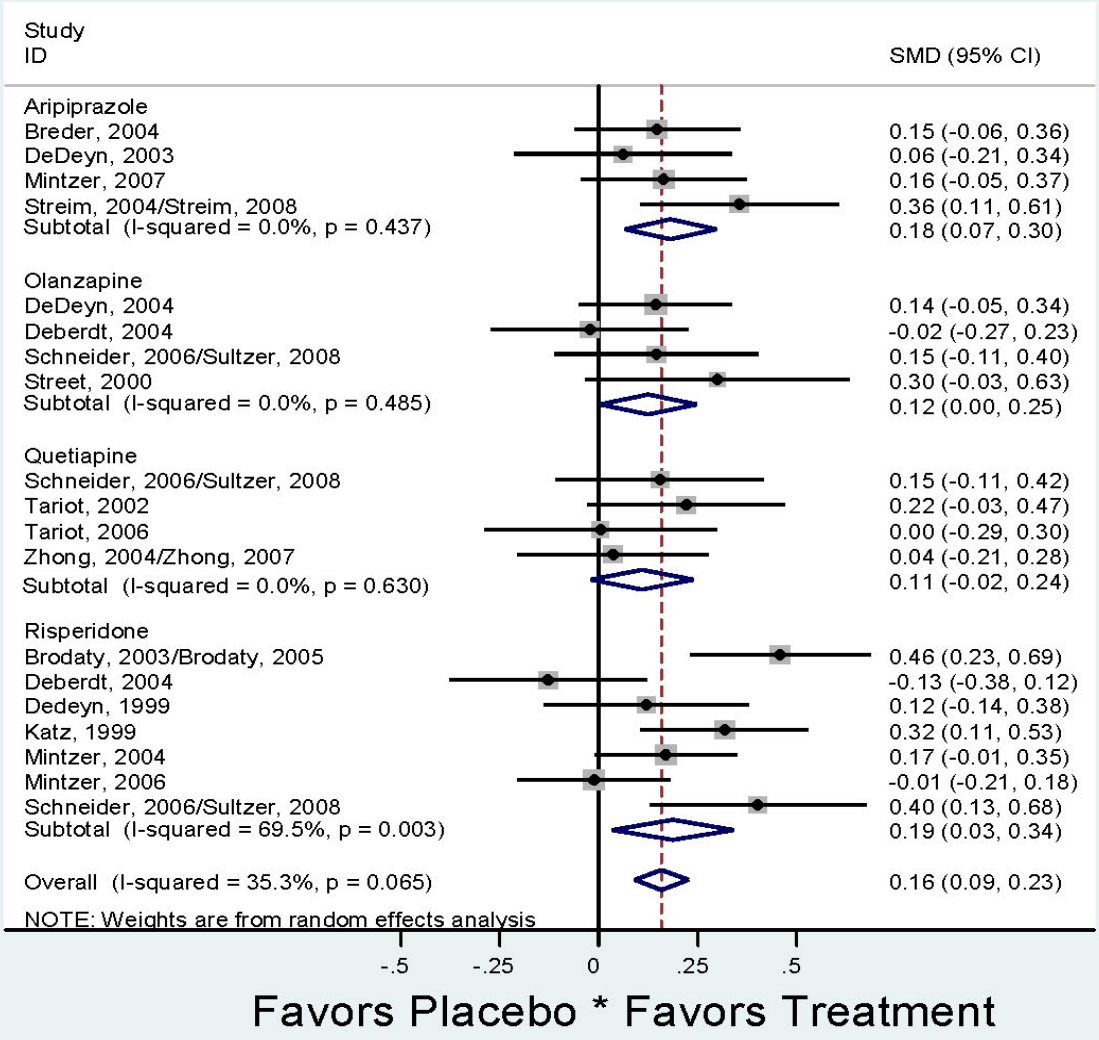


Figure 5. Dementia Placebo Comparisons – Psychosis

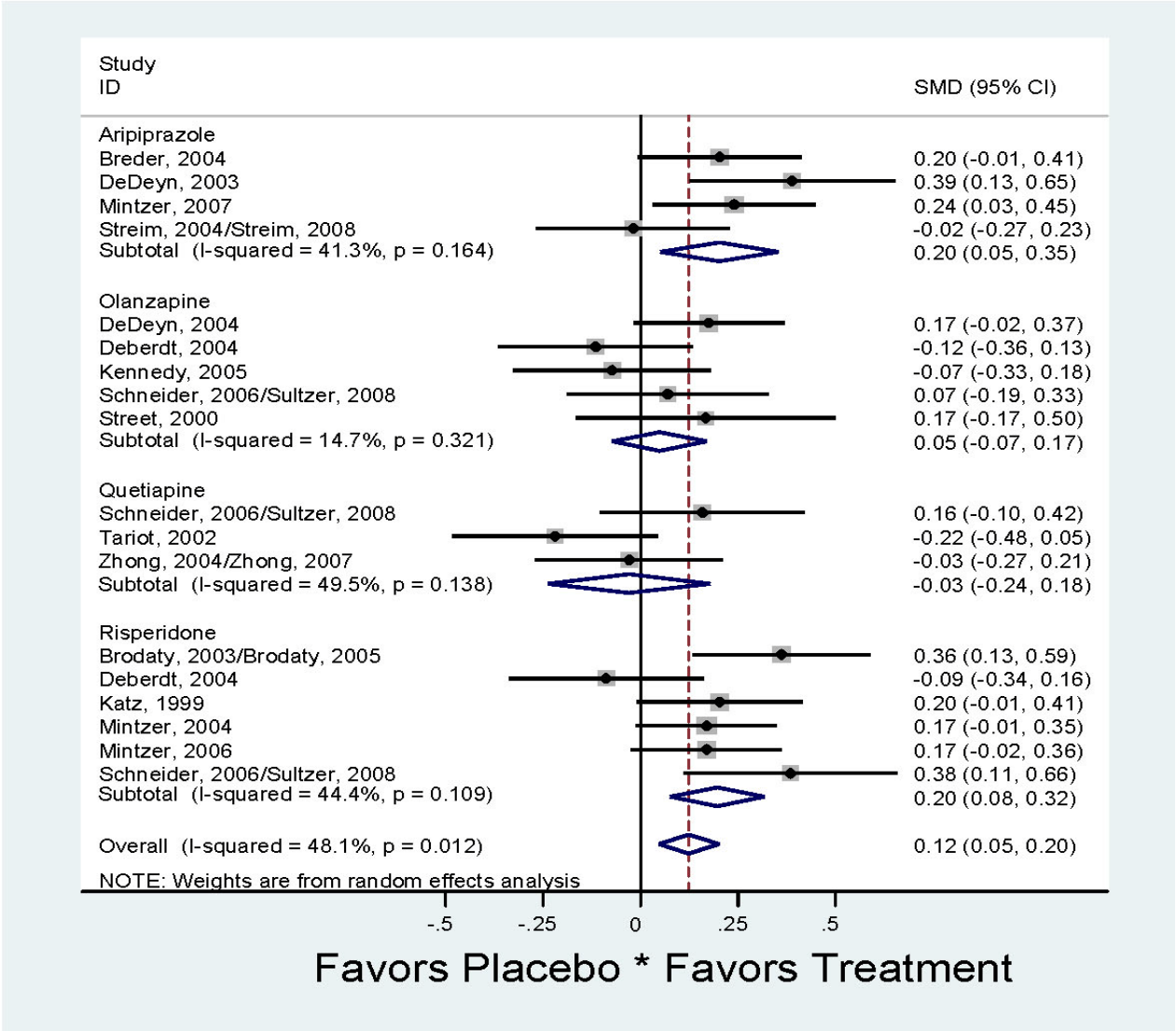


Figure 6. Dementia Placebo Comparisons - Agitation

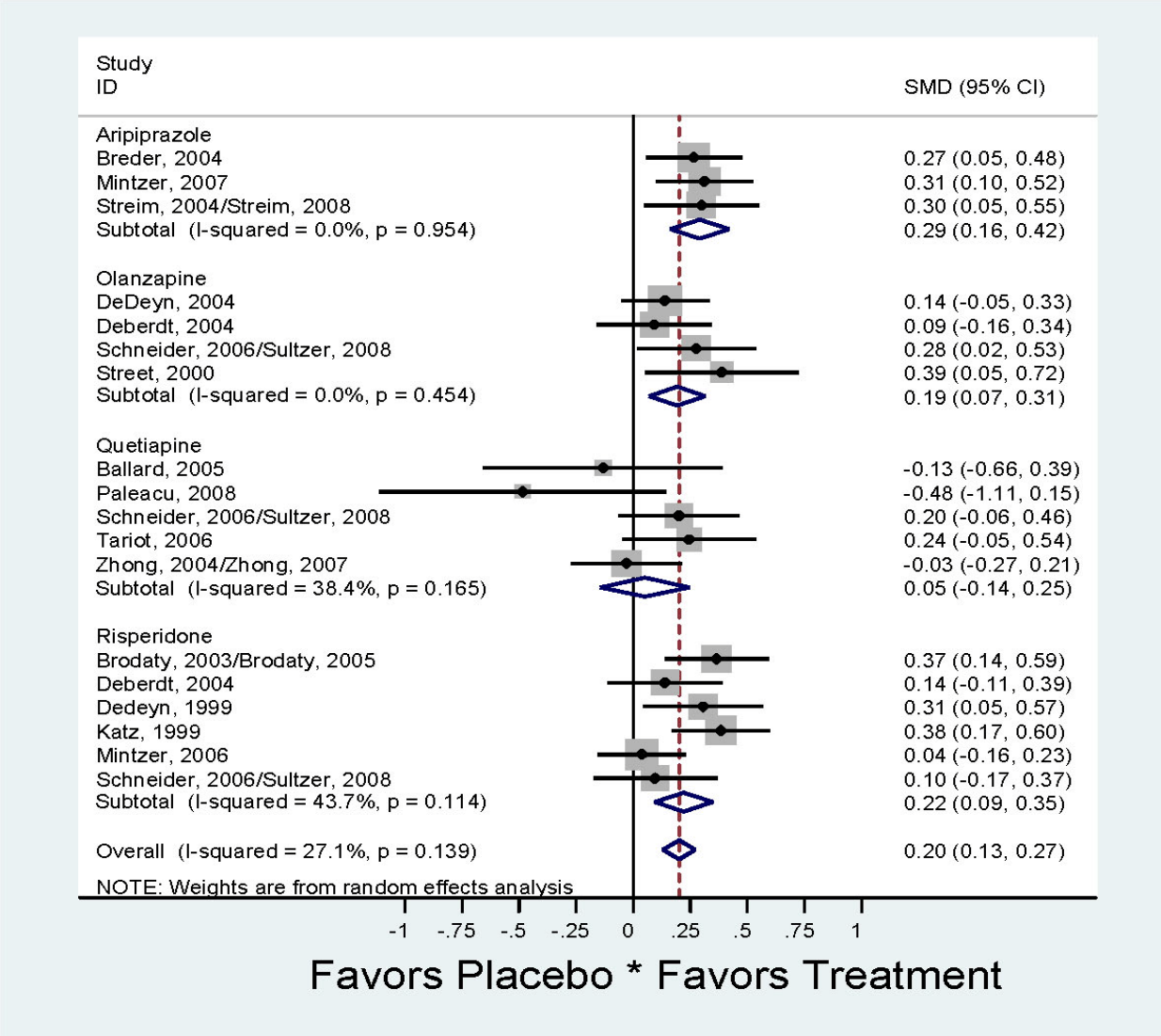


Table 9. Dementia Head-to-head Studies contributing to analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Deberdt et al. 2004[122]	Age >= 40, AD, vascular or mixed dementia, NPI or NPI/NH >= 6 sum of hallucinations and delusional items	494	Placebo Olanzapine-5.2 mg Risperidone-1.0 mg	10 weeks	Total/Global score: Olanzapine vs Risperidone-Standardized Mean Difference (SMD) = 0.10 (-0.10, 0.30) Psychosis score: Olanzapine vs Risperidone-SMD = -0.03 (-0.23, 0.17) Agitation score: Olanzapine vs Risperidone-SMD = -0.04 (-0.24, 0.16)
Schneider, et al. 2006[101] Sultzer et al. 2008[100]	AD or probable AD, MMSE 5-26, psychosis, aggression, or agitation previous week or at least intermittently for 4 weeks, had a severity rating of at least "moderate" for conceptual disorganization, suspiciousness, or hallucinatory behavior on (BPRS), ambulatory and living at home or in an assisted-living facility	421	Placebo Olanzapine 5.5mg/day Quetiapine 56.5 mg/day Risperidone 1.0 mg/day	12 weeks	Total/Global score: Olanzapine vs Risperidone-SMD = -0.27 (-0.56, 0.02) Quetiapine vs Risperidone-SMD = -0.24 (-0.53, 0.06) Psychosis score: Olanzapine vs Risperidone-SMD = -0.27 (-0.56, 0.02) Quetiapine vs Risperidone-SMD = -0.24 (-0.54, 0.05) Agitation score: Olanzapine vs Risperidone-SMD = -0.17 (-0.12, 0.16) Quetiapine vs Risperidone-SMD = 0.10 (-0.20, 0.39)
Rainer et al. 2007[114]	55-85 years old, dementia, MMSE score 10-26, have a NPI part I score in sub-items relating to delusions, hallucinations, agitation / aggression	72	Quetiapine 50-400 mg/day Risperidone 0.5-4 mg/day	8 weeks	Total/Global score: Quetiapine vs Risperidone-SMD = -0.06 (-0.55, 0.43) Agitation score: Quetiapine vs Risperidone-SMD = -0.17 (-0.66, 0.32)

Figure 7. Dementia Head-to-head Studies Olanzapine or Quetapine vs Risperidone – Total/global scores

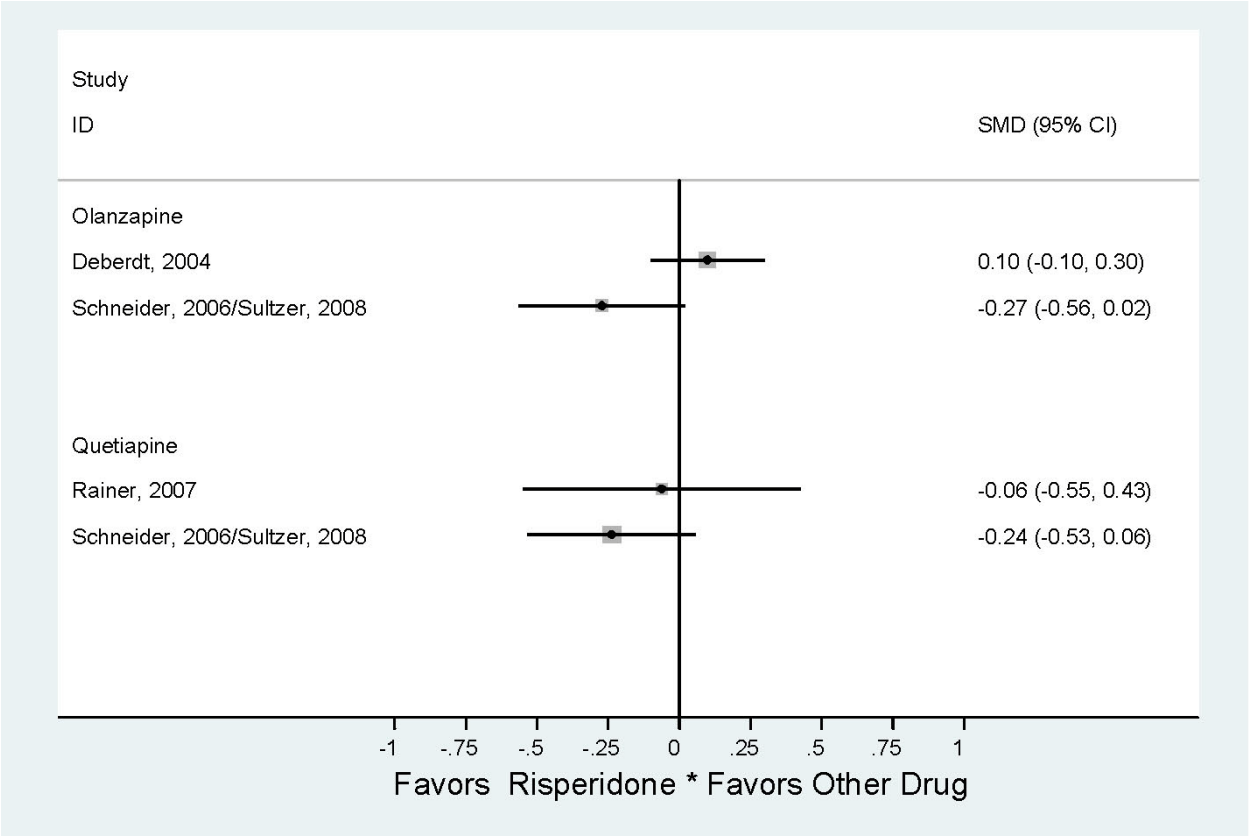


Figure 8. Head-to-head Studies: Olanzapine or Quetapine vs. Risperidone – Psychosis

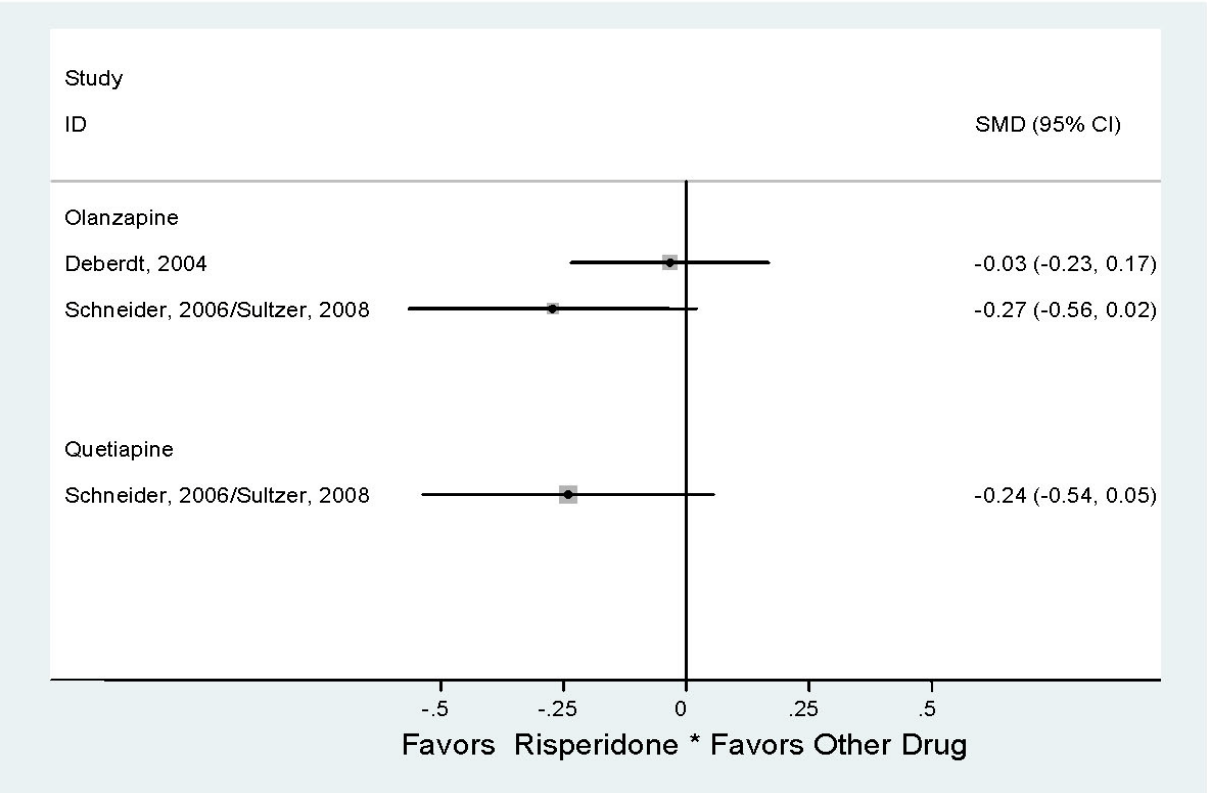


Figure 9. Dementia Head-to-head Studies: Olanzapine or Quetapine vs Risperidone - Agitation

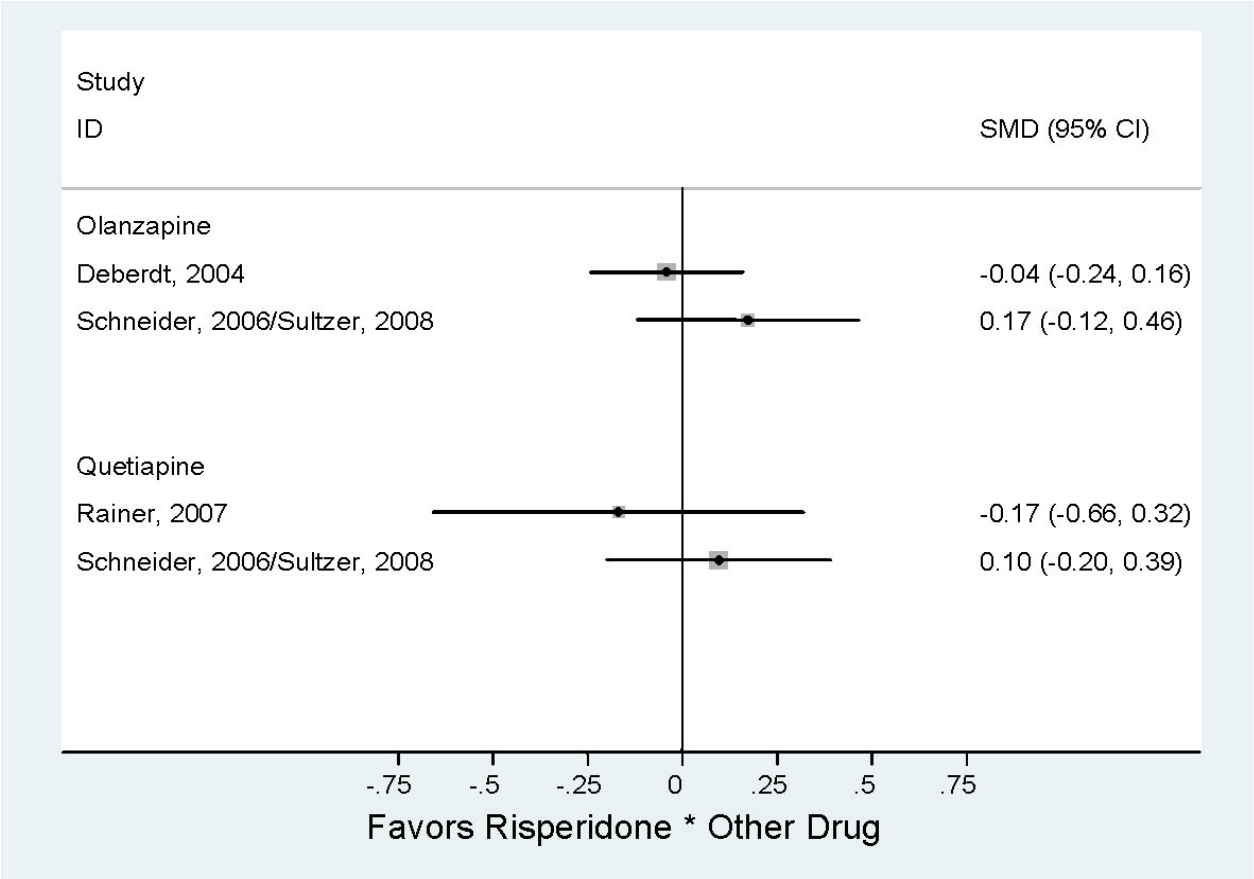


Table 10. Dementia Atypical vs Haloperidol – PCTs contributing to analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Moretti et al. 2005[102]	DSM-IV for dementia, MMSE>=14, probable VaD, 71-92	256	Typical antipsychotics 10 drops/day Olanzapine 2.5-7.5 mg/day	12 months	Total/Global score: Olanzapine vs Haloperidol – Standardized Mean Difference (SMD) = 0.38 (0.17 , 0.60)
Verhey et al. 2006[112]	Age >= 60 years, diagnosis of dementia according to DSM-IV, agitation level requiring antipsychotic treatment, no use of antipsychotic treatment within 3 days of inclusion CMAI score >=45	NR	Haloperidol 1-3 mg/day Olanzapine 2.5-7.5 mg/day	5 weeks	Total/Global score: Olanzapine vs Haloperidol – SMD = -0.18 (-0.77 , 0.41) Agitation score: Olanzapine vs Haloperidol – SMD = -0.21 (-0.73 , 0.31)
Savaskan et al. 2006[108]	AD, behavioral symptoms > 65	NR	Haloperidol 0.5-4 mg/day Quetiapine 25-200 mg/day	5 weeks	Total/Global score: Quetiapine vs Haloperidol – SMD = 0.99 (0.10 , 1.88) Agitation score: Quetiapine vs Haloperidol – SMD = 0.06 (-0.78 , 0.89)
Tariot et al. 2006[105]	> 64 years old, not bedridden, nursing home residents for >= 2 weeks, diagnosed with DSM-IV AD, presence of psychosis, BPRS scores >=24, CGI-S scores >=4, scores of >= 3 on two or more BPRS items, frequency scores of >= 3 on at least one of the two psychosis items of the NPI-NH, scores of >= 5 on MMSE	284	Placebo Haloperidol 0.5-12 mg/day Quetiapine 25-600 mg/day	10 weeks	Total/Global score: Quetiapine vs Haloperidol – SMD = -0.31 (-0.61 , -0.01) Agitation score: Quetiapine vs Haloperidol – SMD = 0.04 (-0.26 , 0.34)
Dedeyn et al. 1999[118]	Age >= 55, Hospitalized/institutionalized, FAST >= 4, MMSE <= 23, BEHAVE-AD behavior pathology > 1, BEHAVE-AD >= 8	344	Placebo Haloperidol 1.2 mg/day Risperidone 1.1 mg/day	12 weeks	Total/Global score: Risperidone vs Haloperidol – SMD = -0.19 (-0.45,0.07) Agitation score: Risperidone vs Haloperidol – SMD = -0.07 (-0.19,-0.33)

Figure 10. Dementia: Atypical vs Haloperidol - Total/Global Scores

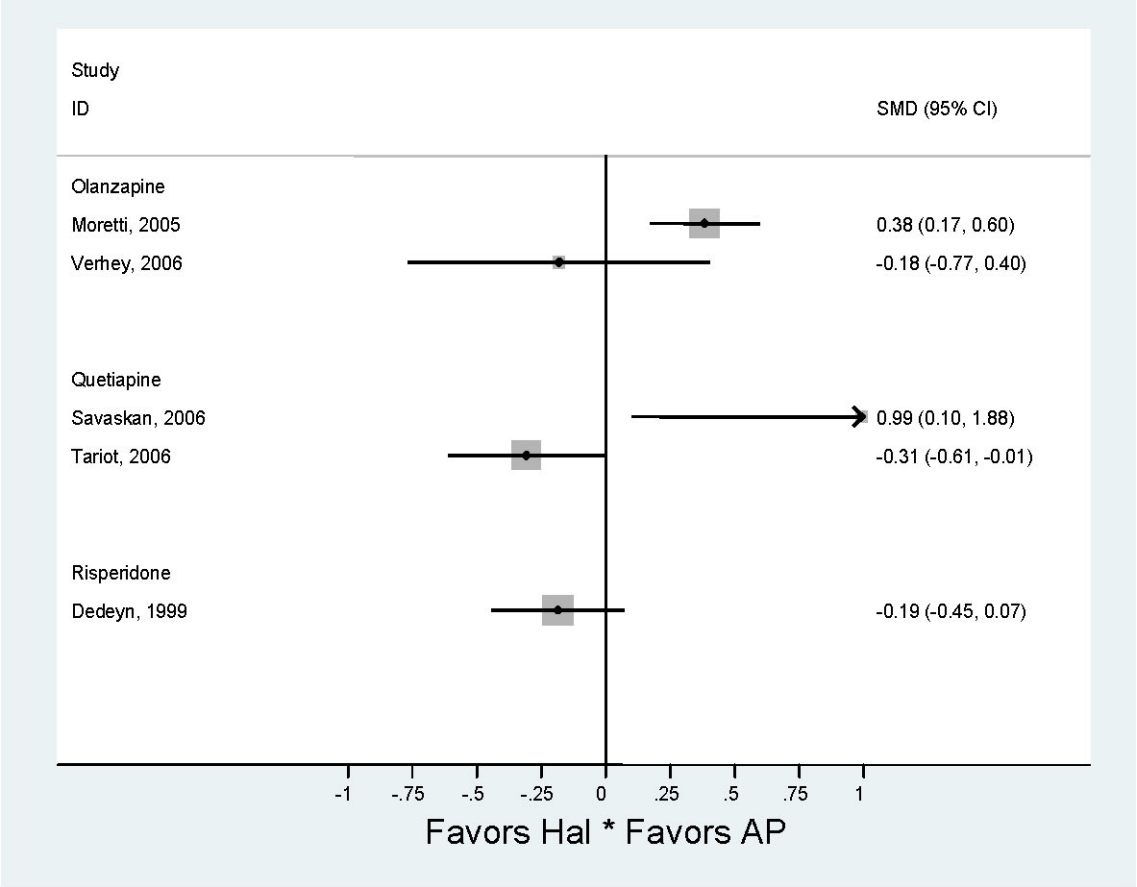
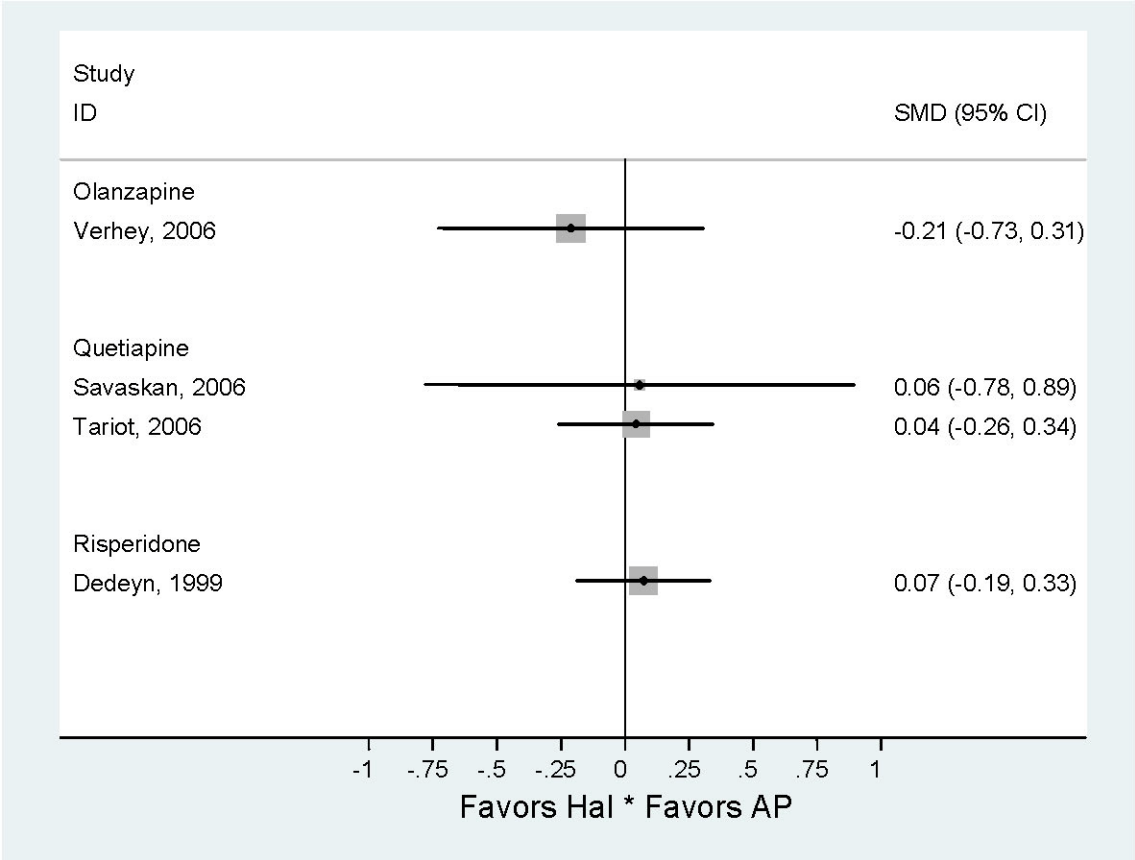


Figure 11. Dementia: Atypical vs Haloperidol - Agitation



DEPRESSION. This section focuses on Major Depressive Disorder (MDD); we excluded other types of depression, including Bipolar Depression or depression with psychotic features. For MDD, our 2006 CER reported that atypicals were not superior to placebo as augmentation to SSRIs at eight weeks. However, in some trials they led to more rapid improvement (two to four weeks). Since then, Papakostas published a meta-analysis on Major Depressive Disorder (MDD) in 2007[130] and updated it in 2009.[131] Both versions found atypicals superior to placebo in increasing response and remission rates, and found no statistical difference between the specific atypicals. Both versions included olanzapine, risperidone, and quetiapine; the most recent version added aripiprazole.

Our literature search identified 33 new reports on the use of an atypical antipsychotic as monotherapy or augmentation for MDD published since our original CER. Six new reports were abstracts, posters or a subset analysis of a trial that we had already identified in our search, so they were not further considered for analysis.[132-137] This left 27 trials. Quality of trials ranged from one to five on the Jadad scale; mean score was 2.7. Sample sizes were usually large; with the mean close to 200. Follow-up times ranged from four weeks to a year.

Of the 27 total trials, four were placebo controlled trials (PCTs) of aripiprazole,[138-141] 14 were PCTs of quetiapine,[142-143 78, 144-154] and five were PCTs of risperidone.[155-157 158-159] One quetiapine PCT augmented treatment with cognitive behavioral therapy (CBT).[143] The results of this trial were suggestive of an added benefit of quetiapine over placebo. However, it was not considered for further analysis as it was deemed to be insufficiently similar to the other studies.

Four other trials were not placebo controlled[160-163] and thus could not be included in our pooled analyses. We describe them here narratively. One study included two parallel eight week double blind trials comparing treatment with a combination of olanzapine and fluoxetine versus olanzapine alone versus fluoxetine alone.[160] The authors report that the pooled results of the two studies found significant differences in mean change of MADRS scores for the olanzapine/ fluoxetine combination, compared to either fluoxetine or olanzapine alone. Another trial evaluated quetiapine versus lithium for 56 days and found greater improvement with quetiapine, according to HAM-D, MADRS and Wildlocher Psychomotor Retardation Scales scores.[161] An eight week trial compared zisprasidone at differing levels augmenting sertraline to sertraline alone.[162] This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAM-D 17, CGI-I, or HAM-A scores. The final non-placebo controlled trial compared quetiapine as augmentation of paroxetine or venlafaxine to venlafaxine or paroxetine alone.[163] This 12 week trial found an improvement in HAMD-17 scores for all groups, with the quetiapine- paroxetine combination showing the greatest improvement, followed by the quetiapine-venlafaxine combination, then paroxetine only and finally venlafaxine only.

Outcomes consistently reported in the remaining 22 PCTs included the Hamilton Depression Rating Scale (HAM-D) total score, percent responders and percent remitted, and the Montgomery-Asberg Depression Rating Scale (MADRS) total score, percent responders and percent remitted. Several trials reported both HAM-D and MADRS outcomes.[141, 145-150, 152-154, 157]

Sixteen trials reported at least one of the HAM-D outcomes and 18 trials reported at least one of the MADRS outcomes. Since the information needed to calculate an effect size for the mean MADRS and HAM-D total scores was not consistently reported, we pooled the percent responded and remitted on each scale. The outcomes were measured between 4 and 8 weeks, considered sufficiently clinically similar to pool. Several PCTs contained more than one treatment arm; these studies compared the effects of different doses of atypicals. For our main efficacy analyses, we pooled these arms together and present one resulting intervention outcome per trial. We present the results by dosage later in the relevant section (Key Question Five).

Three trials that only reported continuous outcomes were thus not included in pooled analysis.[138, 152, 156] The first of these studied risperidone augmentation of antidepressant medication and found a significant decrease in suicidal ideation with risperidone versus placebo.[156] The second compared quetiapine monotherapy with placebo and found that quetiapine significantly increased the time to a depressed event, compared to placebo.[152] The third compared aripiprazole augmentation of an antidepressant to placebo augmentation. They reported a significantly greater change in MADRS total score in those receiving aripiprazole.[138]

One study which reported outcomes at the first depressed event was also not considered for pooled analysis.[151] In that study, the risk of a depressed event was significantly reduced by quetiapine monotherapy, compared to placebo. Additionally, one study did not report outcome data by arm, only overall, so was not included in pooled analysis.[155] In that study, risperidone augmentation of antidepressant therapy was reported to result in symptomatic remission in a substantial number of patients with chronic resistant depression, compared to placebo.

Of the remaining 17 trials, 11 were considered clinically similar to pool using at least one of the MADRS outcomes,[139-141, 147, 150, 153 144, 146, 148-149, 154] five were considered clinically similar to pool using at least one of the HAM-D outcomes,[78, 142, 145, 158-159] and one trial was pooled in both the HAM-D and MADRS analyses.[157] All were augmentation trials. The patient populations were reviewed by a psychiatrist to determine level of severity, age, co-morbid illness and other factors to verify that these populations were indeed similar enough to pool. Additionally, there were two trials (from one article[164]) from the original evidence report that were able to be pooled in HAM-D meta-analyses giving us a total of eight trials contributing data. The PCTs included in our analyses are listed in Tables 11 and 12.

The results of the meta-analyses are displayed in Figures 12 to 15. A person was considered remitted if their HAM-D score was less than or equal to seven (on the HAM-D 17) or a less than or equal to eight (on the HAM-D 24) for two consecutive visits. The eight trials that reported the number of participants classified as remitters using the HAM-D ranged in duration from four to eight weeks.[78, 142, 145, 157-159, 164] The size of these trials ranged from 34 to 274. Only quetiapine and risperidone had a sufficient number of studies to pool estimate of effect by drug. The random effects pooled estimate of the relative risk of remitting on the HAM-D for those treated with quetiapine versus placebo was 2.76 (95% CI 1.21, 6.28), and for those taking risperidone was 2.10 (95% CI 1.43, 3.09). This is equivalent to a NNT (number needed to treat) of five quetiapine and eight for risperidone.

Responders on the HAM-D were identified in the same eight trials. A responder was defined as someone who had at least a 50% reduction in HAM-D score from randomization to follow up. We were only able to calculate a pooled estimate of effect for quetiapine and risperidone, as olanzapine had only two trials. The random effects pooled estimate of the relative risk of responding on the HAM-D for participants taking quetiapine compared to placebo was 2.30 (95% CI 1.35, 3.92), while for risperidone it was 1.50 (95% CI 1.20, 1.87). This is equivalent to an NNT of three for quetiapine and seven for risperidone. The overall I-squared statistic for these eight trials indicated no heterogeneity (0.0%). Neither Begg's nor Egger's test were statistically significant (p=0.711,p=0.245, respectively).

On the MADRS scale the definition of a remitted participant differed slightly between trials. A person was considered remitted if their MADRS score was from eight to ten, depending on the study. The 12 trials that reported the number of participants classified as remitters ranged in duration from four to nine weeks.[146, 148, 157 149 139-141, 144, 147, 150, 153-154] The size of these trials ranged from 87 to 541. Only aripiprazole and quetiapine had a sufficient number of studies to report the pooled estimate of effect per drug. The random effects pooled estimate of the relative risk of remitting on the MADRS for those treated with aripiprazole versus placebo was 1.57 (95% CI 1.24, 2.00); for those taking quetiapine it was 1.35 (95% CI 1.08, 1.69). The overall

pooled estimate for the relative risk of remitting when taking one of these atypical antipsychotics was 1.44 (95% CI 1.30, 1.60). NNT is eleven for both aripiprazole and quetiapine. The overall I-squared statistic for these 12 trials was 64.5%, indicating some heterogeneity. Both Begg's and Egger's test for publication bias were statistically significant (p=0.007,p=0.019, respectively).

Responders on the MADRS were identified in all but one of the trials that reported remitters.[144] These 11 trials ranged in size from 95 to 541. A responder was defined as someone who has at least a 50% reduction in MADRS score from randomization to follow up. We were able to calculate a pooled estimate of effect for aripiprazole and quetiapine, but risperidone was only included in one trial. The random effects pooled estimate of the relative risk of responding on the MADRS for those participants taking aripiprazole compared to placebo was 1.66 (95% CI 1.37, 2.01); for quetiapine it was 1.45 (95% CI 1.25, 1.68). NNT for aripiprazole is seven and quetiapine is six. The overall I-squared statistic for these 11 trials indicated some heterogeneity (52.8%). Both Begg's and Egger's test were statistically significant at the p<0.1 level (p=0.087,p=0.096, respectively).

Table 11. Depression – Placebo-controlled augmentation trials contributing to HAM-D meta-analysis

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Rothschild et al. 2004[164]	MDD,Age ≥ 18, HAM-D ≥ 20	124	Placebo Olanzapine 5-20 mg/day	8 weeks	HAM-D % Remitted: Olanzapine vs Placebo – Relative Risk (RR)=1.45 (0.42, 5.07) HAM-D % Responded: Olanzapine vs Placebo – RR= 1.25 (0.68, 2.28)
Rothschild et al. 2004[164]	MDD, Age ≥ 18, HAM-D ≥ 20	125	Placebo Olanzapine 5-20 mg/day	8 weeks	HAM-D % Remitted: Olanzapine vs Placebo – RR= 1.09 (0.40, 3.00) HAM-D % Responded: Olanzapine vs Placebo – RR= 1.14 (0.64, 2.02)
Mattingly et al. 2006[145]	Outpatients aged 18-65 years old, a primary diagnosis of MDD who were not psychotic, baseline HAM-D 17 >= 20 following a >= 6 weeks SSRI or SNRI treatment, HAM-D item I score >= 2 had failed >= 1 r-week trial of clinically appropriate dose of another antidepressant	40	Placebo 200-400 mg/day Quetiapine 200-400 mg/day	8 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 2.83 (0.73, 10.98) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.12 (0.89, 5.05)

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
McIntyre et al. 2007[78]	18-65, MDD, HAM-D 17 >= 18, CGI-S >=4, HAM-A >= 14, treated with single SSRI/venlafaxine at a therapeutic dose >= 6 weeks	58	Placebo Quetiapine 50-600 mg/day	8 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 1.78 (0.53, 5.97) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.00 (0.76, 5.26)
Zheng et al. 2007[142]	Diagnosed with MDD without psychotic symptoms, HAM-D score >= 18, BPRS item 4 score <= 4, item 11 score <=3, had been treated unsuccessfully with >= 2 different types of antidepressants for >= 6 weeks	NR	Placebo Quetiapine 50-200 mg/day	4 weeks	HAM-D % Remitted: Quetiapine vs Placebo – RR = 8.44 (1.17, 60.94) HAM-D % Responded: Quetiapine vs Placebo – RR = 2.90 (1.13, 7.47)
Gharabawi et al. 2006[159]	Adult outpatients with DSM-IV MDD, had an incomplete response to >= 8 weeks of antidepressant treatment	274	Placebo 0.25-2 mg/day Risperidone 0.25-2 mg/day	6 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 2.03 (1.10, 3.75) HAM-D % Responded: Risperidone vs Placebo – RR = 1.44 (1.03, 2.01)
Keitner et al. 2009[157]	Depressed, failed current antidepressant trial. MADRS >=15, 18-65	97	Placebo Risperidone 0.5-3 mg/day	4 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 1.95 (0.88, 4.33) HAM-D % Responded: Risperidone vs Placebo – RR = 1.49 (0.83, 2.68)
Mahmoud et al. 2007[158]	18-65, antidepressant monotherapy >= 4 weeks, MDD, CGI-S >=4	274	Placebo Risperidone 0.25-2 mg/day	6 weeks	HAM-D % Remitted: Risperidone vs Placebo – RR = 2.29 (1.22, 4.30) HAM-D % Responded: Risperidone vs Placebo – RR = 1.57 (1.20, 1.87)

Figure 12. Depression – HAM-D % Remitted

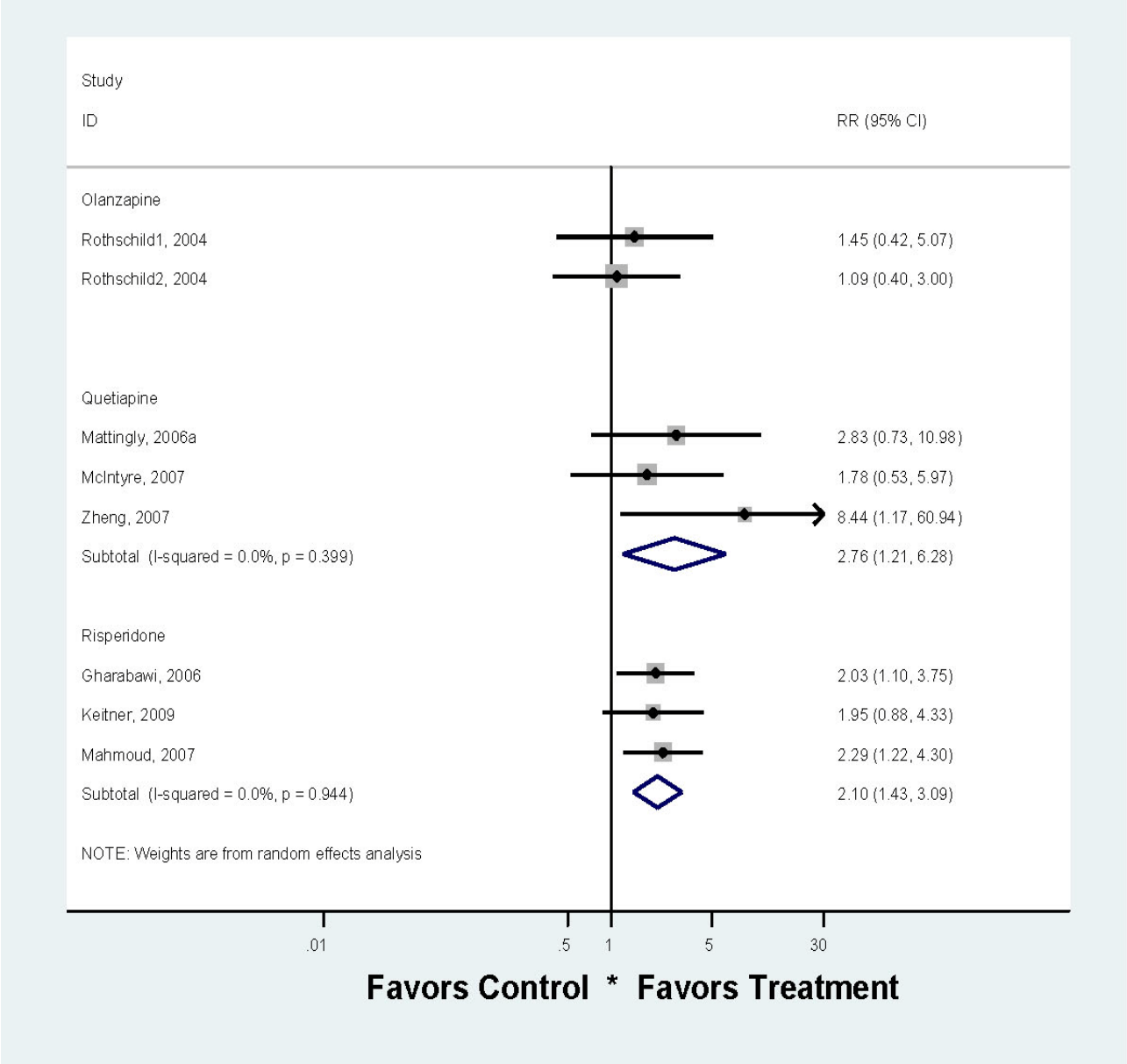


Figure 13. Depression – HAM-D % Responded

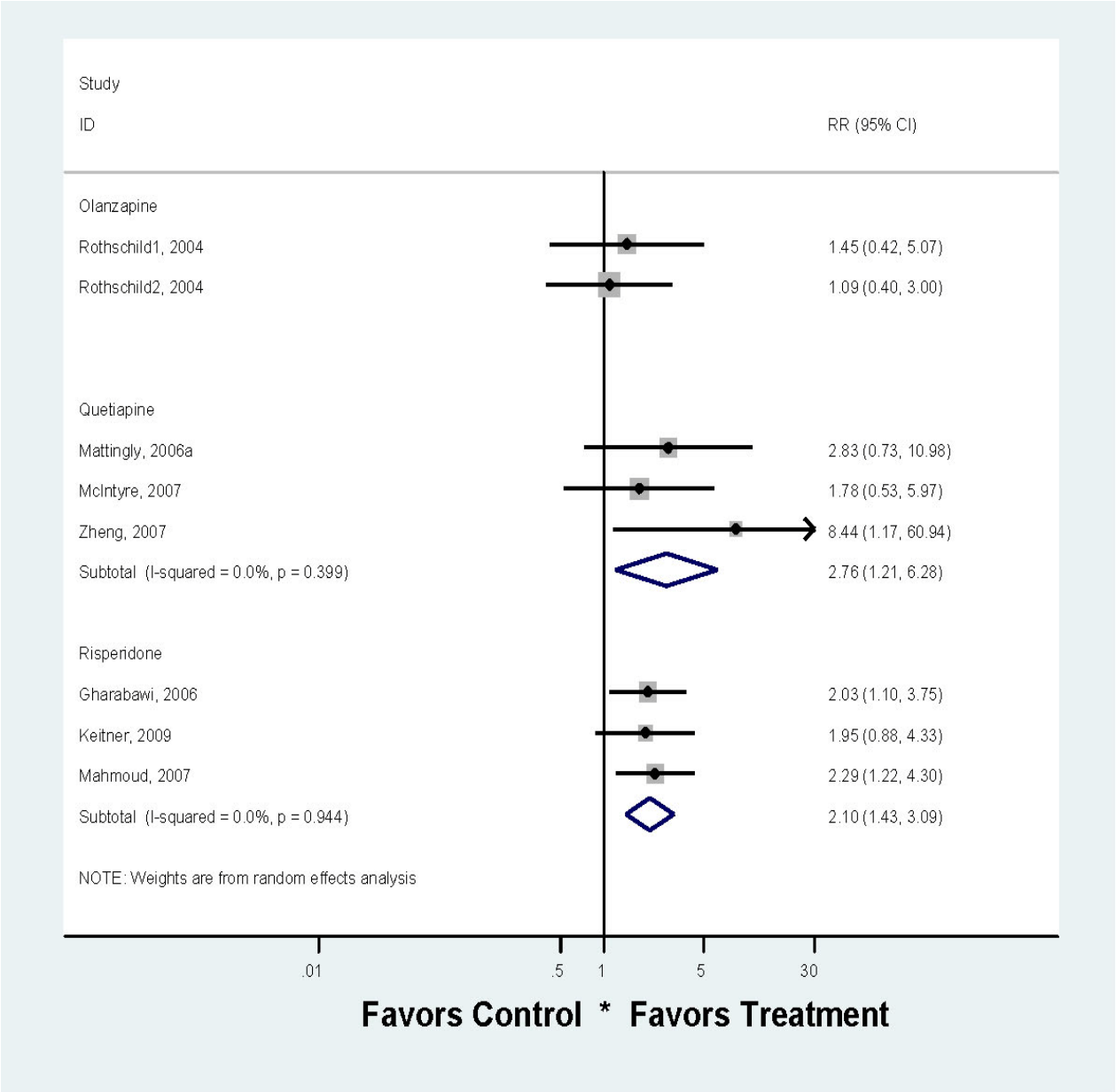


Table 12. Depression – Placebo-controlled augmentation trials contributing to MADRS meta-analysis

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Berman et al. 2007[140]	Diagnosed MDD >=8 weeks, inadequate response to antidepressant, (<50% reduction in depressive symptoms severity), HAM-D-17 >=18	362	Placebo Aripiprazole 2-20 mg/day	6 weeks	MADRS % Remitted: Aripiprazole vs Placebo - Relative Risk (RR) =1.65 (1.08 , 2.53) MADRS % Responded: Aripiprazole vs Placebo – RR = 1.41 (1.01 , 1.98)
Berman et al. 2009[141]	18-65 years old, diagnosed major depressive episode >= 8weeks, inadequate response to previous antidepressants	349	Placebo Aripiprazole 2-20 mg/day	8 weeks	MADRS %: Aripiprazole vs Placebo - RR = 1.43 (0.96 , 2.12) MADRS % Responded: Aripiprazole vs Placebo – RR = 1.75 (1.30 , 2.35)
Marcus et al. 2008[139]	18-65 years old, major depressive episode > = 8weeks, inadequate response to previous antidepressants	382	Placebo Aripiprazole 2-20 mg/day	6 weeks	MADRS % Remitted: Aripiprazole vs Placebo - RR = 1.67 (1.10 , 2.54) MADRS % Responded: Aripiprazole vs Placebo – RR = 1.86 (1.37 , 2.01)
AstraZeneca 2007[147]	18-65 years old, DSM-IV diagnosis of MDD, confirmed by MINI, have been on treatment with an antidepressant >=6 weeks, HAM-D total score >= 20, HAM-D item 1 score >= 2 at both enrollment and randomization.	446	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo – RR = 1.58 (1.15 , 2.19) MADRS % Responded: Quetiapine vs Placebo – RR = 1.58 (1.15 , 2.19)
AstraZeneca 2007[150]	18-65 years old, DSM-IV diagnosis of MDD, HAM-D score >=22, HAM-D item 1 score >=2	471	Placebo Quetiapine 50-300 mg/day Escitalopram 10-20 mg/day	9 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.01 (0.75 , 1.37) MADRS % Responded: Quetiapine vs Placebo – RR = 1.18 (0.97 , 1.45)
AstraZeneca 2008[153]	Age >=66, DSM-IV diagnosis of MDD confirmed by MINI. HAM-D total score >=22, HAM-D item 1 score >=2 at both enrollment and randomization.	338	Placebo 50-300 mg/day Quetiapine 50-300 mg/day	9 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 2.48 (1.70 , 3.62) MADRS % Responded: Quetiapine vs Placebo - RR = 2.11 (1.63 , 2.71)
AstraZeneca 2008[154]	18 -65 years old, MDD confirmed by the MINI and DSM-IV, have a HAM-D >= 22, HAM-D item1 score >= 2 at both enrollment and randomization	310	Placebo 50-300 mg/day Quetiapine 50-300 mg/day	8 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.39 (0.97 , 1.98) MADRS % Responded: Quetiapine vs Placebo - RR = 1.29 (1.05 , 1.59)

Author, Year	Subjects	N	Augmentation	Duration	Outcomes
Bauer et al. 2009[148]	18-65 yrs old, diagnosed MDD, outpatients, HAM-D total score >= 20. HAM-D item I score >= 2, inadequate response during current episode to antidepressants.	493	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.42 (1.03 , 1.94) MADRS % Responded: Quetiapine vs Placebo – RR = 1.22 (1.01 , 1.48)
Cutler et al. 2009[146]	18-65 years old, diagnosed MDD, HAM-D total score >=22, HAM-D item 1 score >=>= at enrollment and randomization	612	Placebo Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day Duloxetine 60 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.43 (1.03 , 2.06) MADRS % Responded: Quetiapine vs Placebo - RR = 1.51 (1.20 , 1.91)
Garakani et al. 2008[144]	18-65 years old, diagnosis of unipolar major depression without psychotic features, MADRS score > 15 at both screen and baseline	114	Placebo 25-100 mg/day Quetiapine 25-100 mg/day	8 weeks	MADRS % Remitted: Quetiapine vs Placebo – RR = 0.87 (0.67 , 1.13)
Weisler et al. 2009[149]	18-65, output, MDD, HAM-D item 17>=22, HAM-D item 1>=2	723	Placebo Quetiapine 50 mg/day Quetiapine 50-150 mg/day Quetiapine 50-300 mg/day	6 weeks	MADRS % Remitted: Quetiapine vs Placebo - RR = 1.27 (0.89 , 1.82) MADRS % Responded: Quetiapine vs Placebo – RR = 1.58 (1.24 , 2.02)
Keitner et al. 2009[157]	Depressed, failed current antidepressant trial. MADRS >=15, 18-65	97	Placebo Risperidone 0.5-3 mg/day	4 weeks	MADRS % Remitted: Risperidone vs Placebo - RR = 2.13 (1.11, 4.08) MADRS % Responded: Risperidone vs Placebo - RR = 1.65 (0.97 , 2.80)

Figure 14. Depression – MADRS % Remitted

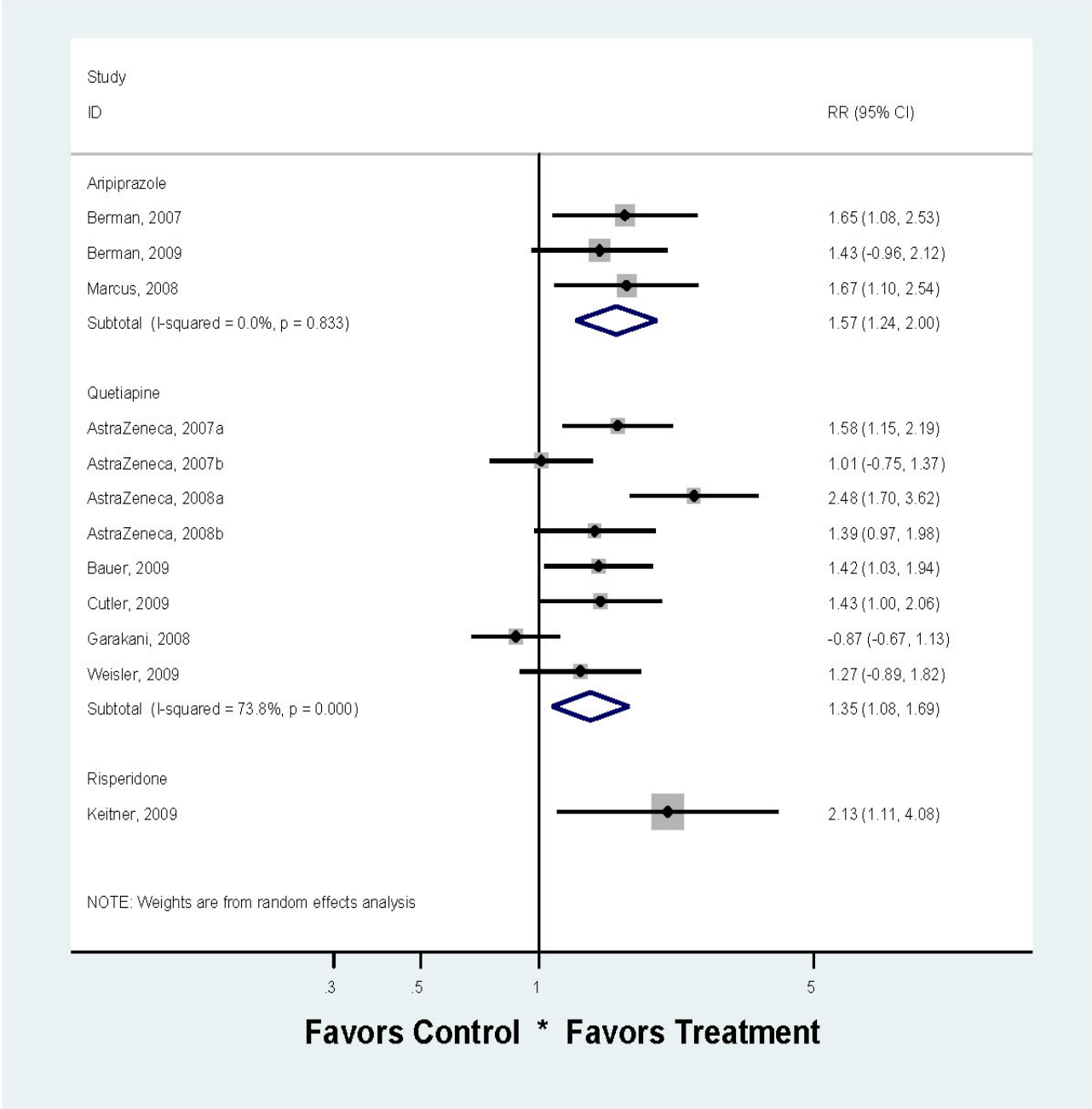
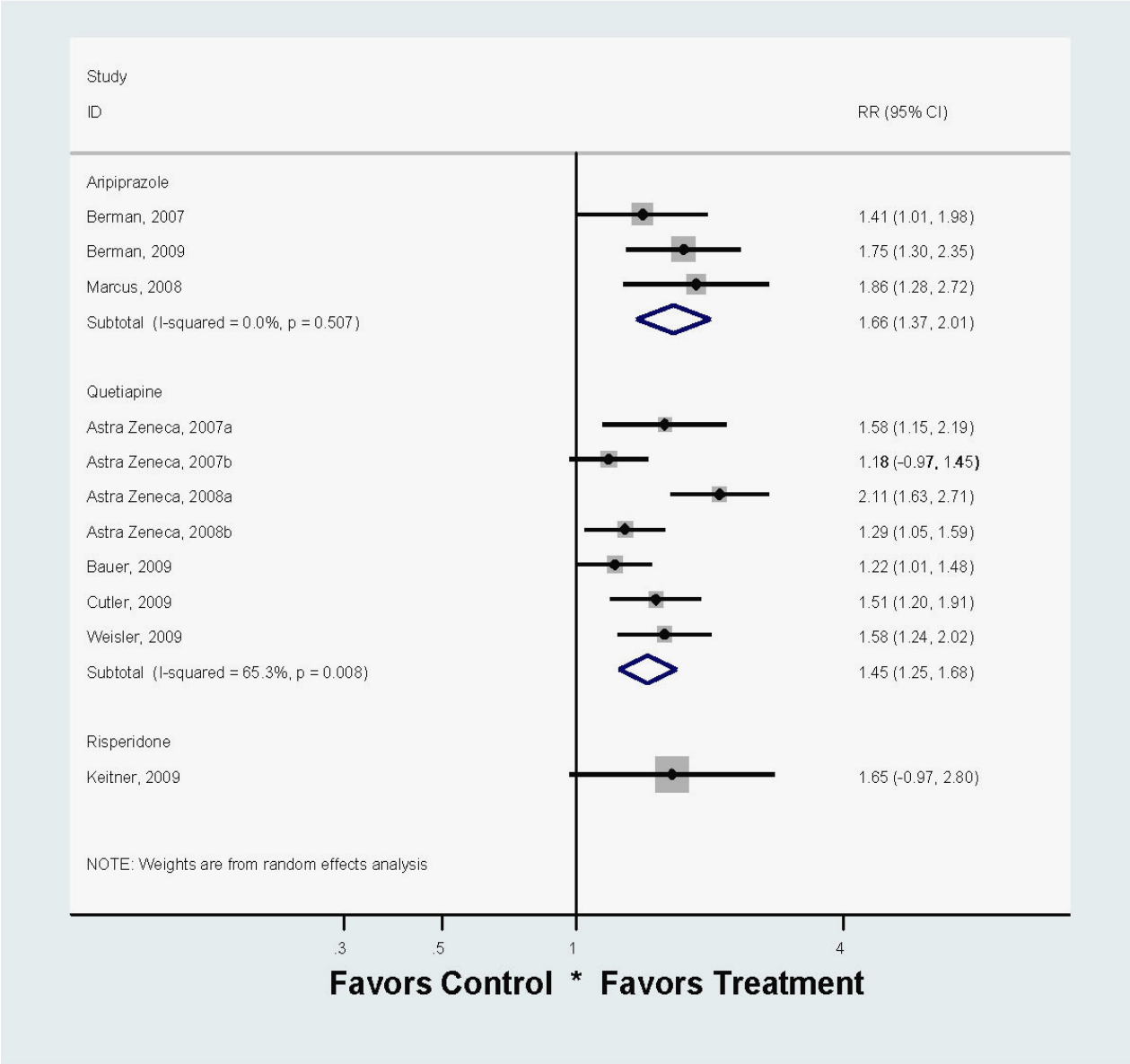


Figure 15. Depression – MADRS % Responded



EATING DISORDER. This off-label use was not included in our 2006 systematic review. We found no published meta-analyses or systematic reviews on this topic. Our literature search identified five trials that assessed olanzapine for this use.[165-169] Mean quality score was 2.0 on the Jadad scale. Trials ranged in length from two to three months. Sample sizes were small, with 15 to 45 participants, per trial. All of the RCTs were placebo-controlled except for one small head-to-head trial that compared olanzapine to a conventional antipsychotic, chlorpromazine,[166] in which the olanzapine group had a significant reduction in anorexic rumination. This trial was excluded from quantitative analysis, which included only placebo comparisons.

Three of the four remaining studies reported body mass index (BMI) at multiple times between one and 13 weeks. One study that only reported weight gain per week was excluded from further analysis.[169] In that study, there were no differences in weight gain by whether or not they were treated with olanzapine.

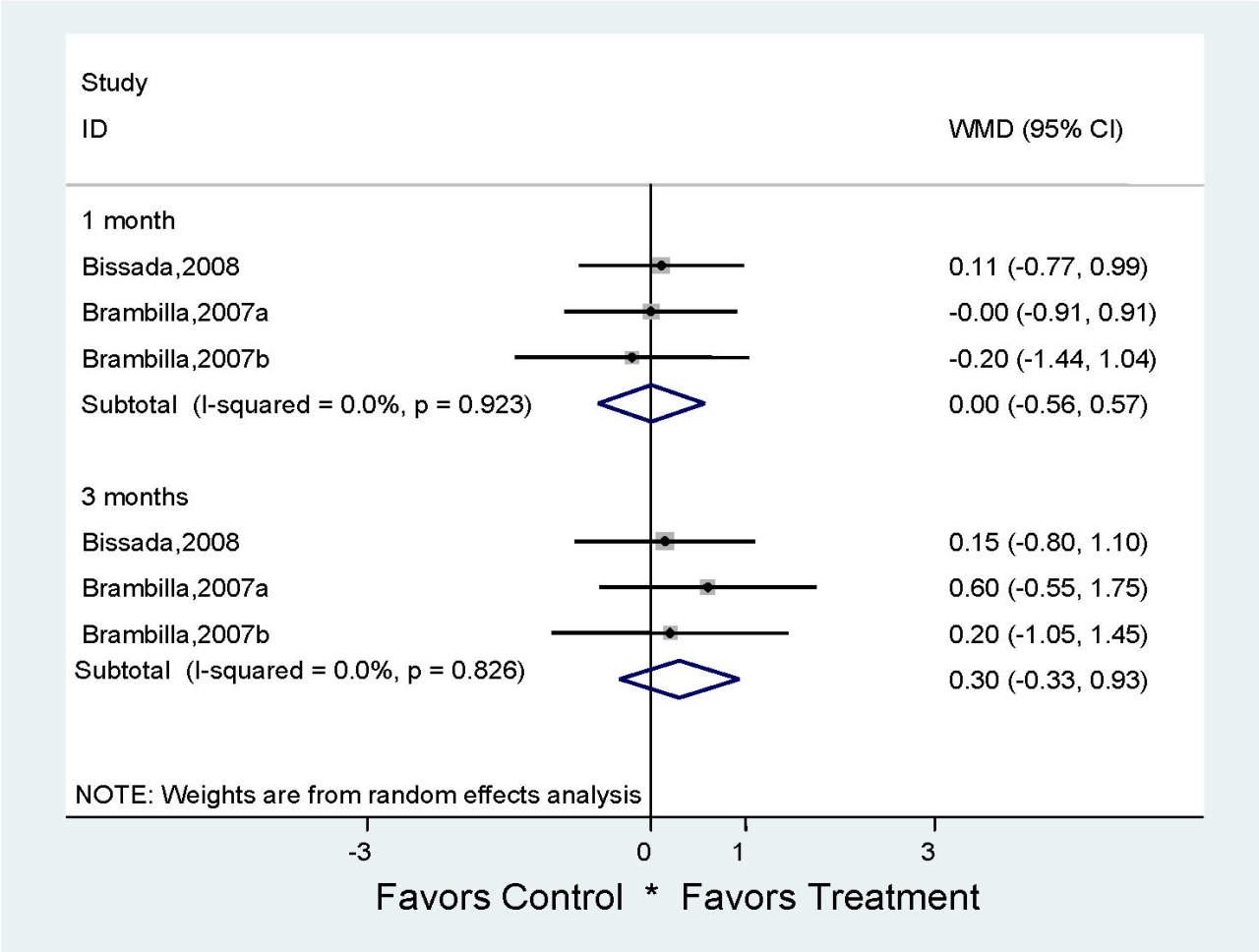
The sample size of the three remaining trials ranged from 20 to 34. These trials were deemed clinically similar to justify meta-analysis at one and three months. [165, 167-168] (BMI is measured such that the desired effect is an increase.)

The random effects pooled weighted mean difference in BMI from baseline to one month of treatment with olanzapine was .004 (95%CI -0.56, 0.57). At three months the random effects pooled estimate was 0.299 (95% CI -0.33, 0.93). (Figure 16) The I-squared statistic for each time point indicated low heterogeneity. Neither Begg's or Egger's test for publication bias were statistically significant at either time point (1 month p=0.30, p=0.21 respectively; 3 months p=1.00, p=0.73 respectively).

Table 13. Eating Disorder – PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Bissada et al. 2008[165]	DSM-IV criteria for anorexia nervosa (restricting or binge / purge subtype) including a body index <= 17.5 kg/m2	34	Placebo Olanzapine 2.5-10 mg/day	10 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo– Weighted Mean Difference (WMD) = 0.11 (-0.77 , 0.99) Change in BMI at 12 weeks: Olanzapine vs. Placebo - WMD = 0.15 (-0.80 , 1.10)
Brambilla et al. 2007[167]	Anorexia nervosa per DSM-IV, restricted or binging-purging type	30	Placebo Olanzapine 2.5-5 mg/day	12 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo- WMD = -0.00 (-0.91 , 0.91) Change in BMI at 12 weeks: Olanzapine vs. Placebo- WMD = 0.60 (-0.55 , 1.75)
Brambilla et al. 2007[168]	Anorexia nervosa according to DSM-IV	20	Placebo Olanzapine 2.5-5 mg	12 weeks	Change in BMI at 4 weeks: Olanzapine vs. Placebo - WMD = -0.20 (-1.44 , 1.04) Change in BMI at 12 weeks: Olanzapine vs. Placebo - WMD = 0.20 (-1.05 , 1.45)

Figure 16. Eating Disorders – BMI



INSOMNIA. This off-label use was not included in our 2006 CER. We found no meta-analyses, systematic reviews, or controlled trials that reported on the use of atypical antipsychotics for insomnia treatment. Thus, we describe six observational studies identified in our literature search; two utilized olanzapine while four utilized quetiapine. Study characteristics are displayed in Table 14 and 15.

One olanzapine study treated 12 patients with insomnia related to major depressive disorder for three weeks. These patients experienced improvements in sleep efficiency, subjective sleep quality and slow wave sleep.[170] The other olanzapine study included case reports of nine patients with different sleep disorders followed for up to three years. Eight patients experienced improvements in sleep including sleep latency, total sleep time, decreased nightmares and unspecified improvements.[171] In both studies, the dosages ranged from 2.5-10mg each night and measurements were done both subjectively and per polysomnogram.

Quetiapine was used to treat insomnia of various causes including: primary insomnia,[172] insomnia of drug withdrawal,[173] tamoxifen- related insomnia[174] and insomnia of Parkinson's Disease.[175] The dosages ranged from 12.5mg to 225mg each night and the patients were treated

from 6 weeks to 3 months. Sleep was measured both objectively using a polysomnogram[172] and subjectively using the Pittsburgh Sleep Quality Inventory (PSQI),[172, 175] the Italian version of the Insomnia Severity Index Scale (ISI),[174] Speigal Sleep Questionnaire,[173] and the Epworth Sleep Scale.[175] All studies showed improvements in sleep including total sleep time, sleep efficiency,[172] overall quality of sleep,[173] all aspects of sleep,[175] and unspecified improvements.[174] Of note, one study did not show an improvement in sleep latency[172] while two others did.[173, 175]

Table 14. Atypical antipsychotics for Insomnia - Olanzapine

Study/Type	Insomnia Type	N	Dosage/Duration	Measures	Effects/AEs
Estivill, 2004[171] Case series	Unspecified	9	2.5mg-10mg/ Up to 3 years	Polysomnogram (8/9)	Improved sleep latency (3), feeling of good sleep (2), total sleep time (3). Decreased nightmares (1). Unspecified improvement (3). No improvement (1)
Sharpley, 2005[170] Open label	Insomnia in major depressive disorder unresponsive to SSRI treatment	12	2.5-10mg (mean 4.8mg)/ 3 weeks	Polysomnogram	Improved sleep efficiency, subjective sleep quality, slow wave sleep

Table 15. Atypical antipsychotics for Insomnia - Quetiapine

Study/Type	Insomnia Type	N	Dosage/Duration	Measures	Effects/AEs
Juri, 2005[175] Case series	Insomnia of Parkinson's Disease	14	12.5-50mg (mean 31.9mg)/ Up to 3 months	Pittsburgh Sleep Quality Inventory (PSQI), Epworth Sleep Scale	All aspects of sleep improved, greatest improvement in sleep onset, daytime sleepiness improved
Pasquini, 2009[174] Case series	Tamoxifen-related insomnia	6	25-100mg/ 6 weeks	Insomnia Severity Index (ISI)- Italian version	"prompt improvement"
Teran, 2008[173] Chart review	Insomnia as main symptom of withdrawal syndrome	52	25-225mg (mean 50mg)/ Up to 60 days	Speigal Sleep Questionnaire	"greatest improvements in overall quality of sleep and time to falling asleep
Wiegand, 2008[172] Open label pilot study	Primary insomnia	18	25-75mg/ 6 weeks	Polysomnogram, PSQI	Improved total sleep time and sleep efficiency

OBSESSIVE COMPULSIVE DISORDER. Our 2006 CER concluded that atypicals have a clinically meaningful benefit when used as augmentation therapy in patients with OCD. That report included a meta-analysis we conducted using the Yale-Brown Obsessive Compulsive Scale (YBOCS) as outcome; both quetiapine and risperidone augmentation increased the odds of response, when compared to augmentation with placebo. (At that time, there were too few trials of olanzapine to permit pooling.) Three other meta-analyses assessing atypical antipsychotics as augmentation for treatment-resistant OCD patients were published around the time of our first evidence report. Two[176-177] included trials of risperidone, quetiapine, and olanzapine. They both found the atypicals have efficacy in increasing the number of responders on the YBOCS. Risperidone was statistically significant, while quetiapine and olanzapine had a trend toward efficacy that was not statistically significant. The other meta-analysis included only quetiapine; the authors pooled two trials and found the drug superior to placebo, as measured by changed in total YBOCS score.[178]

Our literature search identified nine reports of trials published after our 2006 CER.[179-187] Trials were relatively small compared to trials for dementia, anxiety, and depression; sample sizes ranged from 18 to 66. Four were controlled trials of an atypical antipsychotic versus another drug, with no placebo group. These trials ranged in duration from two weeks to one year and measured the change in Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) as the primary outcome. One of these trials evaluated the treatment of OCD with olanzapine versus risperidone;[179] it found no statistically significant differences between treatment groups. Another trial evaluated the treatment of OCD with quetiapine versus ziprasidone both adjunctive with an SRI.[180] This trial reported a 80% improvement in Y-BOCS score for the quetiapine group and a 44.4% improvement for the ziprasidone group. Another trial compared an atypical antipsychotic plus SSRI plus cognitive behavioral treatment (CBT) to SSRI alone plus CBT for the treatment of OCD.[183] The last trial evaluated quetiapine plus an SSRI compared to clomipramine plus an SSRI.[185] Quetiapine augmentation produced a significant reduction in the Y-BOCS score, while clomipramine augmentation did not.

The other five trials reported on PCTs of augmentation. These trials ranged in duration from eight to twelve weeks and measured the change in Y-BOCS as the primary outcome measure. Three evaluated the treatment of OCD with quetiapine plus citalopram or placebo plus citalopram,[184, 186-187] two of which reported on the same data.[184, 187] These two studies found that quetiapine augmentation was superior to placebo according to improvement in both Y-BOCS and CGI-I scores. The final two studies evaluated quetiapine plus SRI or placebo plus SRI treatment.[181-182]

These final two new RCTs that evaluated quetiapine augmentation versus placebo[181-182] along with four RCTs identified in our original report that evaluated the same treatment,[188-191] two from the original report that evaluated olanzapine augmentation versus placebo,[192-193] and three from the original report that assessed risperidone augmentation versus placebo[194-196] were deemed sufficiently clinically similar to justify meta-analysis. These trials are displayed in Table 16.

These eleven trials used the Y-BOCS as the primary outcome, classifying ‘responders’ as those achieving a 25 to 35% improvement on the Y-BOCS total score. The sample sizes ranged

from 16 to 41. The outcome 'responders' on the Y-BOCS was measured at six to 12 weeks. A few PCTs[188, 192, 195] reported very wide confidence intervals; these trials were published earlier (2002 to 2004) than the rest.

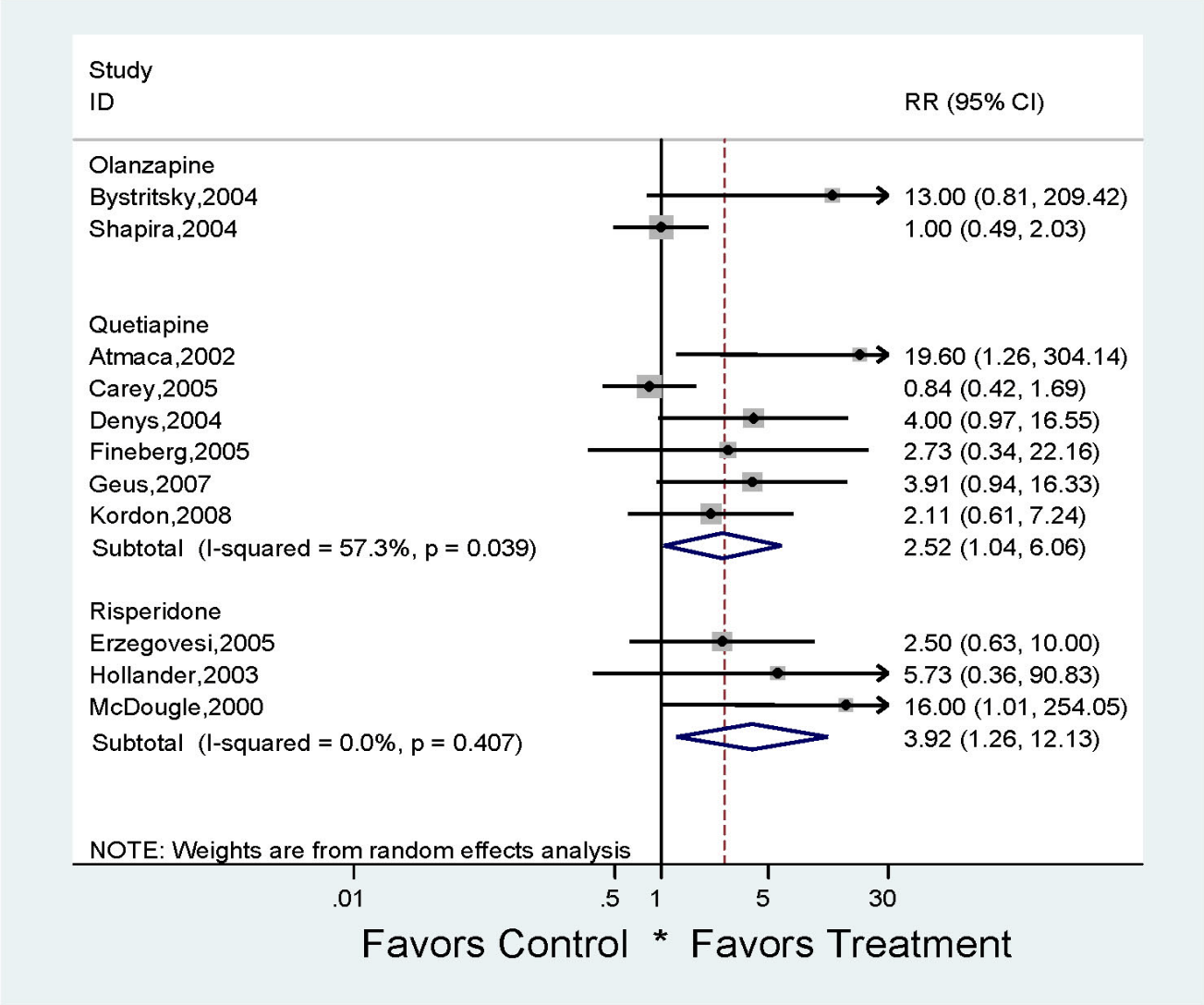
The meta-analysis results are displayed in Figure 17. There were enough studies to calculate a pooled estimate of relative risk for risperidone and quetiapine. The relative risk of 'responding' on the Y-BOCS for those in the quetiapine augmentation arm versus those in the placebo arm was 2.52 (95% CI 1.04, 6.06). The relative risk of 'responding' on the Y-BOCS for those in the risperidone augmentation arm was 3.92 (95% CI 1.27, 12.13). This results in an NNT (number needed to treat) of four for quetiapine and five for risperidone. The I-squared statistic was 54.1%, indicating some heterogeneity. Both Begg's and Eggar's test indicated the possibility of publication bias (p=0.002,p=0.001 respectively).

Table 16. OCD – PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Bystritsky et al., 2004[192]	Age 18-65, OCD	26	Placebo-16.9 mg/day Olanzapine-11.2 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Olanzapine vs Placebo-RR = 13.00 (0.81, 209.42)
Shapira et al. 2004[193]	Age 14-70, 1 year duration primary OCD, CGI >= moderate severity, Y-BOCS >= 19	44	Placebo-5.9 mg/day Olanzapine-6.1 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Olanzapine vs Placebo-RR = 1.00 (0.49, 2.03)
Atmaca et al. 2002[188]	Y-BOCS >= 18, OCD, CGI-I minimal improvement	27	Placebo Quetiapine-91.1 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo- RR = 19.60 (1.26, 304.14)
Carey et al. 2005[190]	Age 18-65, Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, CGI-I minimal improvement, CGI = worse	42	Placebo - 228.57 mg/day Quetiapine - 168.75 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo- RR = 0.84 (0.42, 1.69)
Denys et al. 2004[189]	Age 18-65, Y-BOCS >= 18, Y-BOCS >=12, if only obsessions or compulsions were present, Refractory to SRI therapy	40	Placebo Quetiapine-150 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 4.00 (0.97, 16.55)
Fineberg et al. 2005[191]	Y-BOCS < 25% improvement > 12 wks of SRI treatment at maximum tolerated dose, Y-BOCS >=18	21	Placebo Quetiapine - 215 mg/day	16 weeks (12 week outcome pooled)	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 2.73 (0.34, 22.16)
de Geus et al. 2007[181]	18-65 years old, primary OCD. Y-BOCS total score >= 18 or 12 if only obsessions or compulsions present, failure to respond to previous or current treatment (<= 35% improvement)	39	Placebo Quetiapine 50-300 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 3.91 (0.94, 16.33)

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Kordon et al. 2008[182]	Aged 18-65, diagnosis of OCD, Y-BOCS >= 18, treated with an SRI >= 12 weeks and non-responders (< 25% improvement in Y-BOCS)	40	Placebo 100-600 mg/day Quetiapine 100-600 mg/day	12 weeks	Responders improving 25-35% on Y-BOCS: Quetiapine vs Placebo-RR = 2.11 (0.61, 7.24)
Erzegovesi et al. 2005[194]	Age 18-65, 1 year duration primary condition, Drug-free within 3 weeks, Drug-free for at least 3 wks prior to study entry	45	Placebo Risperidone-0.5 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 2.50 (0.63, 10.00)
Hollander et al. 2003[195]	CGI >= 3,SRI therapy >= 12 weeks, >=2 SRI trials of adequate dose and duration	16	Placebo 2.75 mg/day Risperidone 2.25 mg/day	8 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 5.73 (0.36, 90.83)
McDougle et al. 2000[196]	1 year duration primary OCD, CGI >= moderate severity, Refractory to SRI therapy	36	Placebo Risperidone-2.2 mg/day	6 weeks	Responders improving 25-35% on Y-BOCS: Risperidone vs Placebo-RR = 3.92 (1.26, 12.13)

Figure 17. OCD – Responders improving 25-35% on YBOCS



PERSONALITY DISORDER. Our 2006 CER found promising results for this off-label use. Three PCTs of olanzapine and one of aripiprazole reported efficacy compared to placebo. Since 2006, several additional trials have been published showing mixed results.

In 2010 a meta-analysis on the efficacy of antipsychotics in treatment of personality disorders[197] was published. It included three studies of olanzapine[198-200] and one each of risperidone[201] and aripiprazole.[202] It also included several studies of conventional antipsychotics, and pooled all the antipsychotics together, without separating out the effects of atypicals. Therefore, we will not report the results of this analysis.

Since our initial CER eight trials of personality disorders have been published, seven of which looked at Borderline Personality Disorder. Four of these studies showed an improvement with treatment. Two of these studies involved the same population of patients, first reporting

after 8 weeks of treatment and then again after 18 months. In those studies, aripiprazole was the treatment used.[202-203]

Another study showing improvement used olanzapine and showed improvement when 5-10mg was used each day but no change from placebo when 2.5mg was used.[204] A study reporting only the psychotic symptoms associated with Borderline Personality Disorder found an improvement with quetiapine.[205]

Of note, the three studies that did not show an improvement used ziprasidone or olanzapine and, though there was no difference in response from placebo, both groups of patients in each study showed improvement overall with the treated patients showing a faster time to response.[206-208] Studies were too heterogeneous to perform meta-analyses.

Borderline Personality Disorder – Paliperidone. Our search found only one study of this drug for off-label conditions.[209] Although it is a very small observational study, we thought it was worth mentioning due to lack of any other relevant data on paliperidone.

In that pilot study there were eight patients with borderline personality disorder and no other current interfering psychiatric disorder such as psychotic disorders, bipolar disorder, cognitive disorder, major depression or substance abuse. The patients were given paliperidone ER for 12 weeks in a dose of 3-6mg per day. Of the six patients who completed the study, the publication lists that paliperidone was efficacious in reducing global symptoms and "a few core symptoms" of borderline personality disorder. However, there is no specific data regarding these results. There were reports of adverse effects including EPS, insomnia and agitation and two patients dropped out of the study- one for noncompliance and the other for gastrointestinal adverse effects.

There was one study that looked at cognitive symptoms in Schizotypal Personality Disorder and found no significant difference from placebo in those treated with risperidone.[210] Studies on personality disorder are displayed in Table 17 below.

Table 17. Atypical antipsychotics for Personality Disorder

Study/Type	Disorder/Treatment	N	Dosage/Duration	Measures	Effects/AEs
Nickel, 2006[202]/ RCT	Borderline PD/ aripiprazole	52	15mg/ 8 weeks	SCL-90-R, HAM-D, HAM-A, STAXI	Significant changes on most scales of SCL-90-R, HAM-D, HAM-A and all scales of STAXI/
Nickel, 2007[203]/ Follow-up observation of RCT above	Borderline PD/ aripiprazole	52	15mg / 18 months	SCL-90-R, HAM-D, HAM-A, STAXI	Greater changes on all SCL-90-R scores, less self-injury

Study/Type	Disorder/Treatment	N	Dosage/Duration	Measures	Effects/AEs
Pascual, 2008[206]/ RCT	Borderline PD/ ziprasidone	60	40-200mg (mean 84.1mg)/ 12 weeks	CGI-BPD, HAM-D-17, HAM-A, BPRS, SCL-90-R, Barratt Impulsiveness scale, Buss-Durkee Inventory	No significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms
Schulz, 2008[207]/ RCT	Borderline PD/ olanzapine	314	2.5-10mg (mean 7.09mg)/ 12 weeks	ZAN-BPD, SCL-90-R, GAF, SDS, OAS-M, MADRS	No significant difference from placebo
Linehan, 2008[208]/ RCT	Borderline PD/ olanzapine	24	2.5-15mg (mean 4.46mg) + DBT therapy/ 6 months	OAS-M, TMR, HAM-D, Somatic Symptom Scale	No significant difference from placebo
Zanarini, 2007[204]/ RCT of dose response.	Borderline PD/ olanzapine	451 (150 @2.5m 148@5 -10mg)	2.5-10mg/ 12 weeks	ZAN-BPD	Greater change in ZAN-BPD with 5-10mg of olanzapine
VanDenBroek,2008[205]/ RCT	Borderline PD (psychotic symptoms)/ quetiapine	24	200-600mg/ 8 weeks	BPRS, PANSS, DIS-Q	Superior to placebo on BPRS, PANSS
McClure, 2009[210]/ RCT	Schizotypal PD (cognitive symptoms)/ risperidone	31	0.25-2mg/ 10 weeks	Cognitive assessment battery	No significant difference from placebo

POST TRAUMATIC STRESS DISORDER (PTSD). Our 2006 CER found six PCTs of atypicals for PTSD. Due to heterogeneity, we would not conduct meta-analysis. Trials for combat-related PTSD reported benefits, while trials in abused woman reported mixed results.

A meta-analysis on use of atypical antipsychotics as monotherapy or medication augmentation for patients with PTSD[211] was published after our original evidence report. It included five studies of risperidone[212-216] and two studies of olanzapine.[217-218] It found that atypicals have benefit (compared to placebo) as measured by the change in CAPS (Clinician Administered PTSD Scale) score. The publication did not report separate results by drug or clinical subtype.

Our literature search identified three placebo controlled trials that assessed risperidone for the treatment of PTSD[215, 219-220] that had been published since our CER. Combined with the studies included in the original CER, there were eight studies of risperidone[212-216, 219-221] and two studies of olanzapine[217-218] for PTSD. Trials were small, ranging from 15 to 40 participants. Quality scores ranged from two to four on the Jadad scale.

Two trials identified in the new literature search reported on the same trials we included in our previous report.[215, 220] We selected the most current article to include in our new CER.[215-216] This left eight trials varying in duration from 5 to 16 weeks. All but two of these trials measured

the Clinician-Administered PTSD Scale (CAPS). One that did not utilize the CAPS studied showed no difference in improvement between the olanzapine and placebo group.[218] The other found risperidone superior to placebo in reducing irritability and intrusive thought symptoms of PTSD.[214] One risperidone PCT[215] reported that the treated population showed a significant difference in the CAPS score at endpoint, compared to placebo, but did not report the exact numbers.

Thus, five PCTs, which were clinically comparable, were pooled in our meta-analyses.[212-213, 216-217, 219] The trials are displayed on Table 18. The sample sizes ranged from 19 to 65, while the duration ranged from five to 16 weeks, with three trials reporting results at eight weeks. Risperidone dose ranged from 0.5mg to 3mg daily. The one trial of olanzapine used 15mg daily dose.

The similar outcome across these five trials was the CAPS total score. A lower CAPS score indicates fewer PTSD symptoms. Thus, we calculated a weighted mean difference for each study and a positive weighted mean difference means an improvement in CAPS total score from baseline to follow up.

We stratified our analyses first by drug (Figure 18). Only risperidone had enough eligible studies to calculate a pooled estimate.[212-213, 216, 219] The random effects pooled estimate for risperidone was 6.47 (95% CI 0.32, 12.61). The one olanzapine study[217] had an effect size of 12.13 (95% CI 0.97, 23.29). The overall random effects pooled estimate for risperidone and the one olanzapine study was 7.79 (95% CI 2.40, 13.17), with an I-square = 0.0%. The clinical importance of this 6 or 12 point weighted mean difference needs to be considered in the context that the range of this instrument is zero to 136 points, and the standardized mean differences are 0.40, which is normally considered “moderate” in size.

We also performed a meta-analysis stratified on combat status (Figure 19). We included three studies that included patients with PTSD from combat situations,[212, 216-217] and two studies that primarily included abused women with PTSD.[213, 219] We only had a sufficient number of studies to perform pooled analysis on the combat studies. We found a random effects pooled estimate of 7.95 (95% CI 1.06, 14.84).

Finally, we performed a meta-analysis of the risperidone studies stratified by follow-up time (Figure 20) divided the studies in to durations greater than or equal to 12 weeks or less than 12 weeks. One study reported outcomes in both time frames,[219] one additional study reported outcomes at 12 weeks or more[212] and two additional studies reported outcomes at less than 12 weeks.[213, 216] We only had a sufficient number of studies to report a pooled effect for the less than 12 week outcomes. The random effects pooled estimate for these three studies was not statistically significant (3.23, 95% -5.47, 11.93), indicating that we did not find an improvement in CAPS scores for risperidone treatment over placebo at less than 12 weeks.

Table 18. PTSD – PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Stein et al. 2002[217]	PTSD diagnosis, Refractory to SRI therapy	19	Placebo 20.00 mg/day Olanzapine 15.00 mg/day	8 weeks	Difference in CAPS score: Olanzapine vs. Placebo – Weighted Mean Difference (WMD) = 12.13 (0.97, 23.29)
Bartzokis et al. 2005[212]	Proof of military service, CAPS ≥ 65	65	Placebo Risperidone 3 mg/day	16 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = 9.70 (1.01, 18.39)
Hamner et al. 2003[216]	Age >= 18, Psychosis/psychotic features, PANSS >= 60, PANSS with score ≥ 4 on at least 1 item on positive symptoms subscale	40	Placebo Risperidone-2.5 mg/day	5 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = -1.10 (-14.37, 12.17)
Reich et al. 2004[213]	CAPS-1 >= 50, PTSD related to childhood physical, sexual, emotional or verbal abuse,	21	Placebo Risperidone-1.41 mg/day	8 weeks	Difference in CAPS score: Risperidone vs. Placebo – WMD = 11.00 (-8.55, 30.55)
Rothbaum et al. 2008[219]	18-65, PTSD due to civilian trauma, CAPS >=50	25	Placebo Risperidone 0.5-3 mg/day	8 weeks	Difference in CAPS: Risperidone vs. Placebo – WMD = 4.08 (-10.17, 18.34)

Figure 18. PTSD – By Drug – Difference in CAPS score

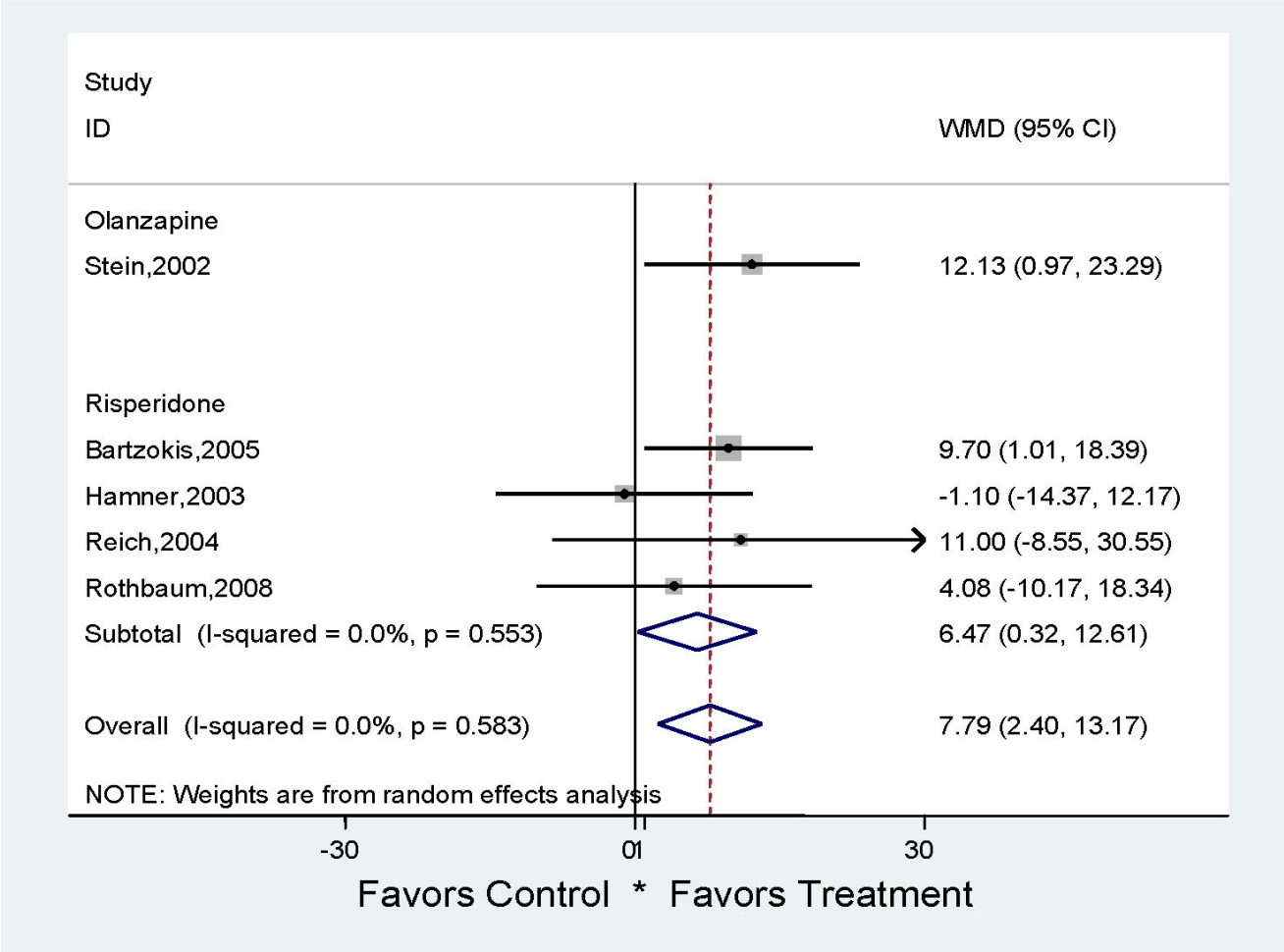


Figure 19. PTSD – By Combat Status – Difference in CAPS score

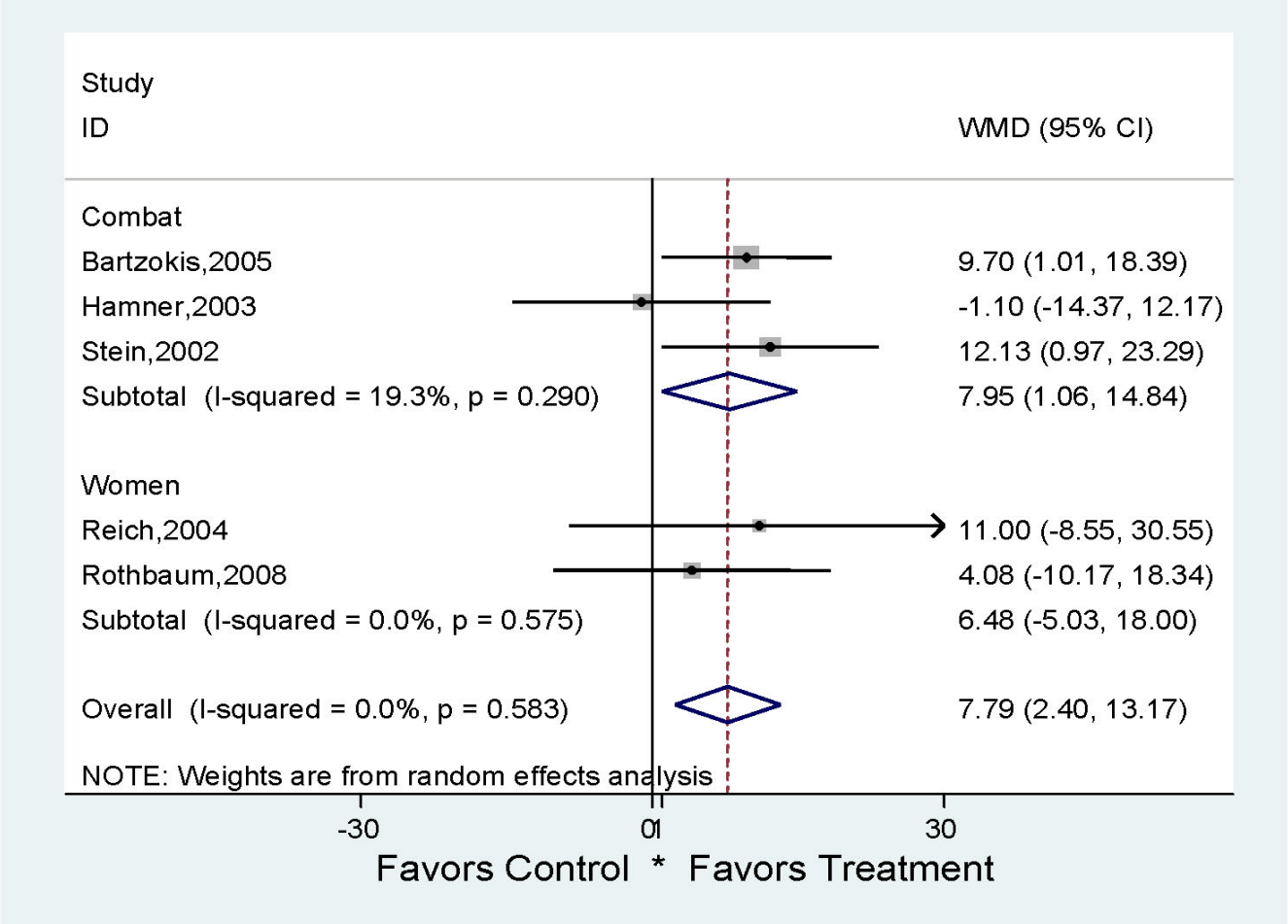
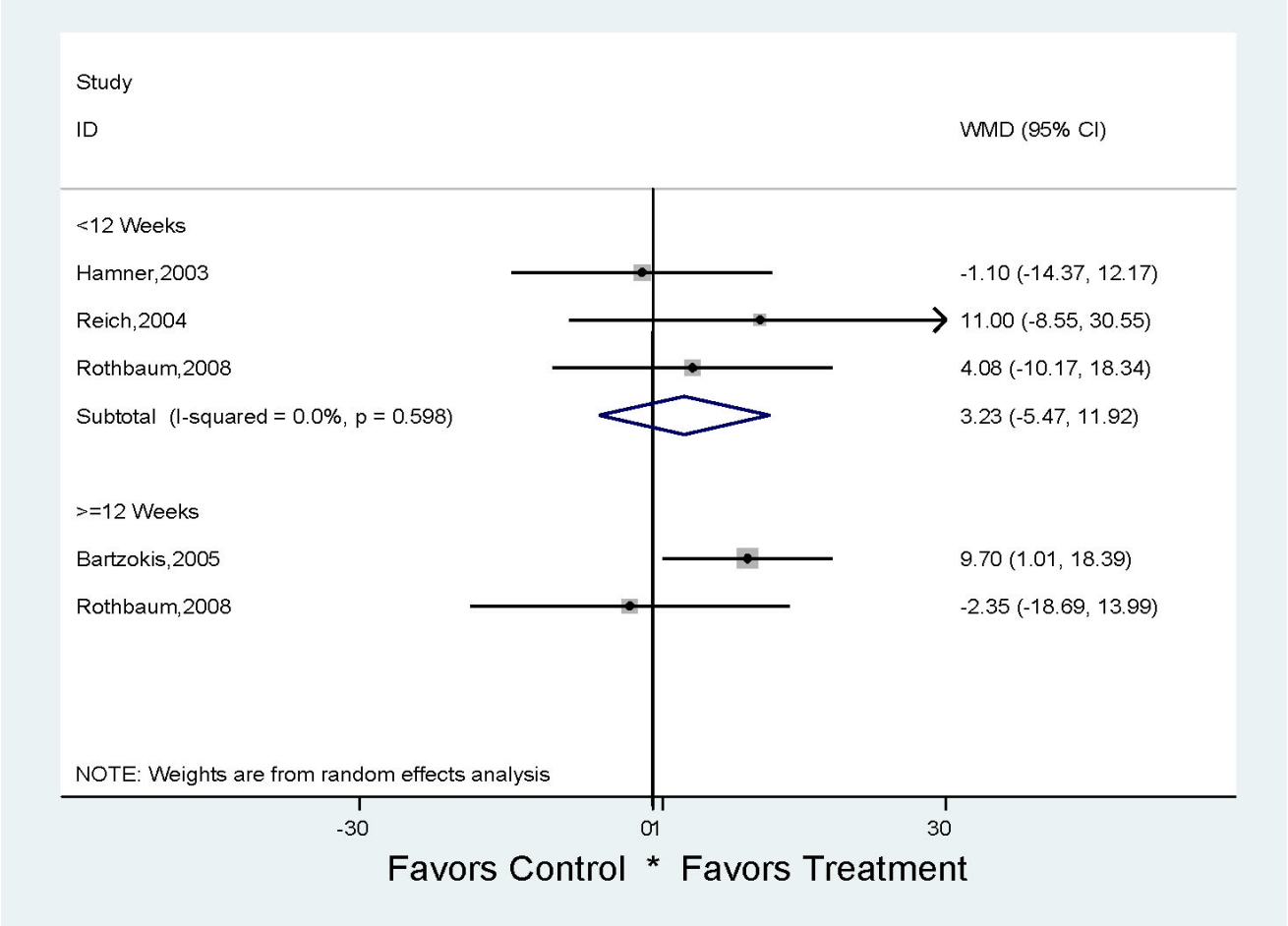


Figure 20. PTSD – By Time – Difference in CAPS score



SUBSTANCE ABUSE. This off-label use was not included in our 2006 CER. Our literature search identified 32 studies that evaluated the use of atypical antipsychotics for this purpose. Nine trials were excluded from further analysis because they included patients with schizophrenia or schizophrenia-related psychosis [222-229] or bipolar disorder.[230]

Of the remaining 23 trials, nine evaluated aripiprazole,[231-234] olanzapine,[235-238] and quetiapine[239] treatment for alcohol abuse and dependence. Ten trials assessed aripiprazole,[240-241] olanzapine,[242-244] and risperidone[245-249] treatment for cocaine abuse and dependence. The quality and size of trials varied widely; Jadad scores ranged from zero to five, and sample size ranged from three to 262 participants.

Two trials assessed aripiprazole versus placebo for amphetamine/methamphetamine abuse[250-251] and one trial evaluated olanzapine versus an SSRI and benzodiazepine for the treatment of heroin abuse and dependence.[252] The two amphetamine/methamphetamine treatment trials found aripiprazole not likely to be an efficacious treatment.[250-251] The heroin treatment trial found olanzapine did not improve addictive behavior or relapse.[252] Another trial assessed treatment of concurrent cocaine and heroin dependence with the combination of methadone with risperidone

at 2 or 4mg or placebo. This trial found no difference in reduction of cocaine or opiate use, between the three groups.[253]

Alcohol. The nine trials that evaluated treatment of alcohol abuse ranged in duration from a few hours to 16 weeks. Two trials reporting on outcomes only after a specified number of drinks or several hours were not included.[235, 238]

The most commonly reported outcome was drinking abstinence, which was reported in six of the remaining seven trials. The one trial[237] that did not report on abstinence compared olanzapine and placebo's effects on alcohol craving. After 2 weeks of treatment, they found that those participants with the longer repeat allele of the DRD4 VNTR gene responded to olanzapine with reduced craving and alcohol use whereas the participants with the shorter alleles did not. One study compared naltrexone with aripiprazole; there was no difference in either mean number of days abstinent or percentage of group completely abstinent.[231]

Of the five trials that reported on abstinence, one did not report sufficient data to calculate an effect size to use in further analyses.[234] In that study, aripiprazole was found no better than placebo on the main outcome of percentage of days abstinent. Of the remaining four trails, two reported only the number or percentage of patients that were completely abstinent at 12 weeks,[232, 239] one reported the number of patients that were completely abstinent and the number or percentage of days abstinent,[232] and one trial reported the number of days abstinent.[236]

We performed meta-analysis for percentage of patient completely abstinent. Results are displayed in Figure 21. Three trials reported the number or percentage of patients completely abstinent during the follow up period, which ranged from 8 days to 16 weeks. Two evaluated aripiprazole[232-233] and one assessed quetiapine.[239] The trials are displayed in Table 19. The size of these trials ranged from 30 to 288 participants. The overall random effects pooled estimate of the relative risk of remaining completely abstinent was 1.42 (95% CI 0.36, 5.67). The overall I-squared statistic was 80.4%. Neither Begg's nor Eggar's test indicated publication bias ($p = .296$, $p = .308$, respectively).

Cocaine. One published meta-analysis[254] assessed use of atypicals in treatment of cocaine dependence. It included three trials of risperidone[247, 249, 253] and three of olanzapine.[225, 243-244] Outcome was rate of drop-out from residential and outpatient substance abuse treatment programs. The analysis found atypicals inefficacious; effect was not reported separately by medication.

Ten trials with placebo comparisons reported on the treatment of cocaine abuse or dependence with aripiprazole,[240-241] olanzapine,[242-244] and risperidone.[245-249] These trials ranged from several days to 20 weeks. Outcomes reported varied greatly; most consistently reported outcomes were the Cocaine Craving Questionnaire (CCQ) and the Addiction Severity Index Drug Composite Score (ASI-drug). Two trials reported neither the CCQ or the ASI;[246-247] they were not considered for further analysis. The first reported that risperidone improved neuropsychological impairment in cocaine-withdrawn patients. [246] The second compared risperidone or pergolide with placebo and found neither more efficacious than placebo in reducing cocaine use. [247]

Five of the remaining eight cocaine abuse treatment trials reported the CCQ.[240-242, 244, 249] None reported useable CCQ data that would allow us to calculate an effect size estimate, thus we could not use the CCQ as a poolable outcome. Five of the eight trials reported the ASI-drug composite score, two of which had no useable data.[242, 245] The first of these compared olanzapine to placebo for 16 weeks. They found that olanzapine was not superior to placebo in decreasing use, cravings or addiction severity.[242] The second of these compared risperidone to placebo in the treatment of cocaine dependence. There was no reduction in cocaine use after 12 weeks of treatment.[245] The remaining three trials were considered comparable enough to justify meta-analysis, pooling on the continuous ASI-drug composite score outcome.[243-244, 248] The trials are listed in Table 20; meta-analyses results are displayed in Figure 22.

These trials of olanzapine[243-244] and risperidone[248] treatment for cocaine abuse ranged in size from 30 to 68 participants and lasted from eight to 12 weeks. We calculated a weighted mean difference for the effect size estimate in which a positive weighted mean difference favors the treatment arm. The overall random effects pooled estimate for the difference in ASI-drug composite score was 0.001 (95% CI -0.41, 0.043). The I-squared statistic indicated no heterogeneity. Neither Begg's nor Eggar's test indicated publication bias (p=1.00,p=0.928 respectively).

Table 19. Alcohol Abuse – PCTs contributing to meta-analyses

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Anton et al. 2008 [232]	21-65 years old, alcohol dependence, present at 3 visits with negative breathalyzer results and abstain from alcohol before randomization Score < 8 on Clinical Institute Withdrawal Assessment for Alcohol Revised	295	Placebo 27.4 mg/day Aripiprazole 2-30 mg/day	12 weeks	Alcohol complete abstinence: Aripiprazole vs Placebo – Relative Risk (RR)= 0.50 (0.29 , 0.88) Abstinent days: Aripiprazole vs Placebo – Standardized Mean Difference (SMD)=-0.13(-0.36, 0.10)
Voronin et al. 2008 [233]	Aged 21-65, alcohol dependence, non treatment seeking	30	Placebo Aripiprazole 5-15 mg/day	8 days	Alcohol complete abstinence: Aripiprazole vs Placebo - Relative Risk (RR)= 1.67 (0.48 , 5.76)
Kampman et al. 2007 [239]	Aged >= 18 years old, alcohol dependence, have a consecutive 30 days period drinking at least 48 standard drinks, >= 2 days of heavy drinking, >= 3 consecutive days of abstinence, Clinical Institutes Withdrawal Assessment for Alcohol score < 8	61	Placebo 50-400 mg/day Quetiapine 50-400 mg/day	12 weeks	Alcohol complete abstinence: Quetiapine vs Placebo - Relative Risk (RR)= 4.97 (1.17 , 21.11)

Figure 21. Substance Abuse – Alcohol Complete Abstinence

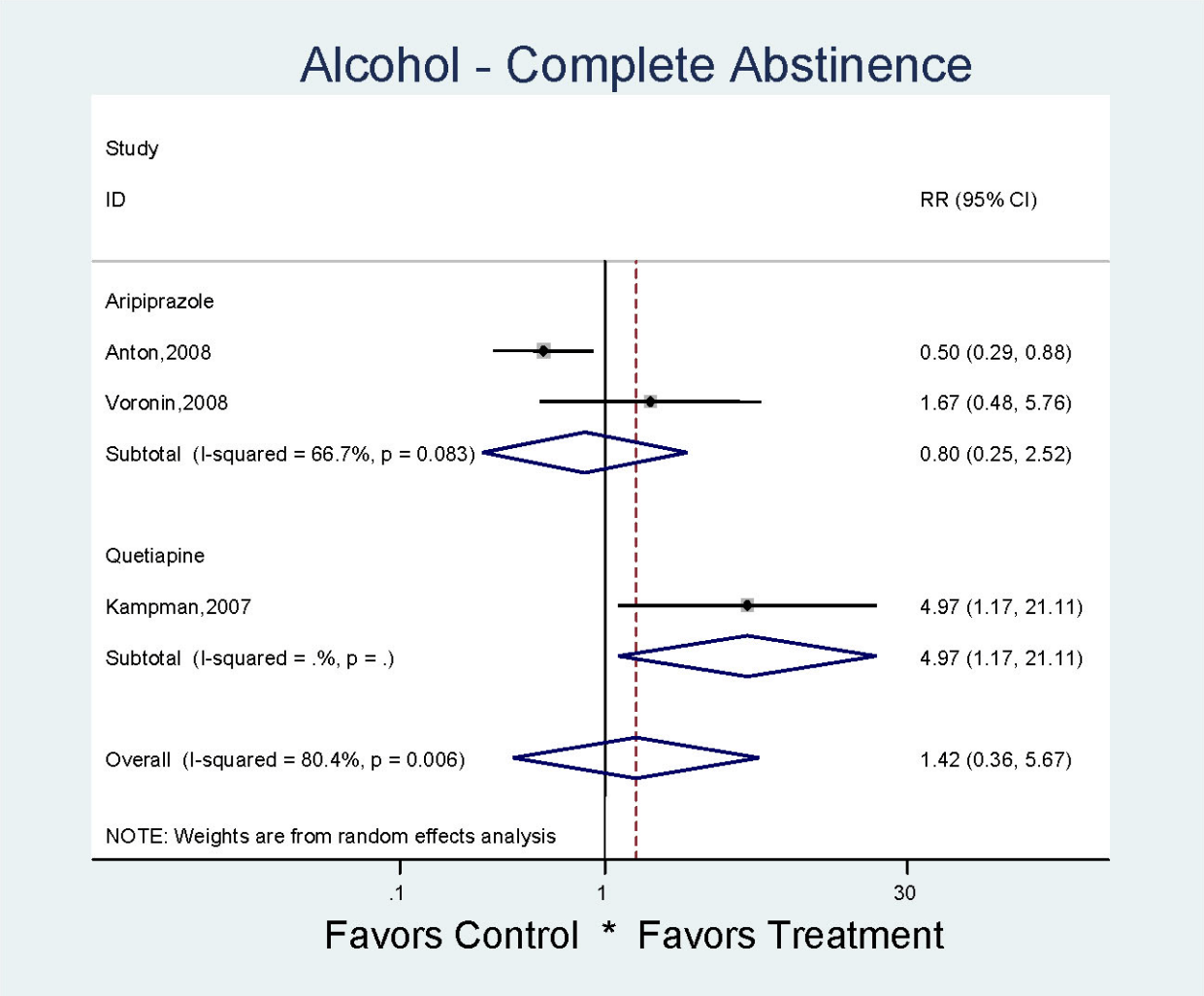
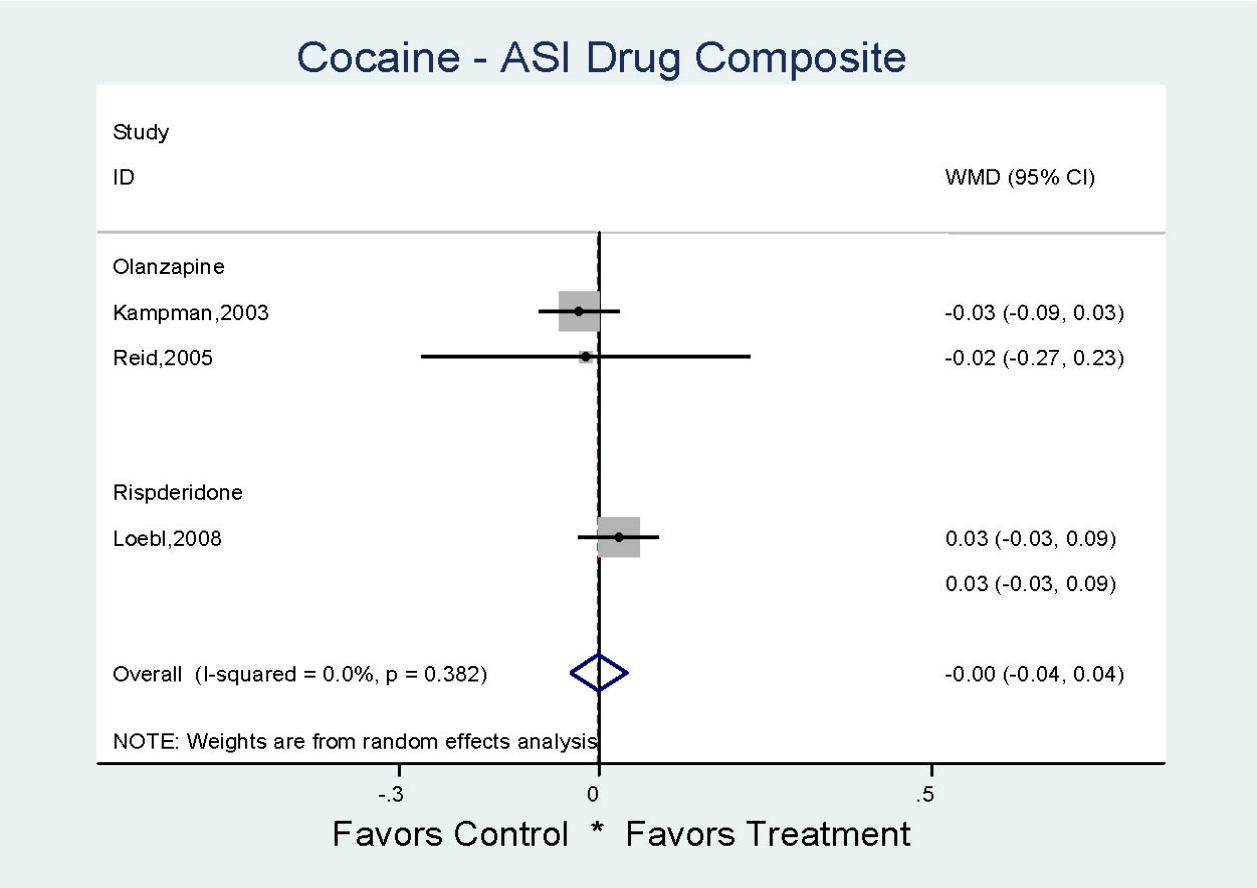


Table 20. Cocaine – PCTs contributing to meta-analysis

Author, Year	Subjects	N	Treatments	Duration	Outcomes
Kampman et al. 2003[243]	$100 worth of cocaine use in prior month, age 18-60, cocaine dependency	30	Placebo 2.5-10 mg/day Olanzapine 2.5-10 mg/day	11 weeks	Change in ASI: Olanzapine vs Placebo – Weighted Mean Difference (WMD) = 0.03 (-0.03 , 0.09)
Reid et al. 2005[244]	Standardized CREST study inclusion criteria	68	Placebo 2 tablets/day Olanzapine 5-10 mg/day Valproate 800-1500 mg/day Carnitine + CoQ 10 200+500 mg/day	8 weeks	Change in ASI: Olanzapine vs Placebo - Weighted Mean Difference (WMD) = 0.02 (-0.23 , 0.27)
Loebl et al. 2008[248]	Men, 18-60, cocaine dependence, using cocaine >=1 every other week	31	Placebo Risperidone 1-2 mg daily	12 weeks	Change in ASI: Risperidone vs Placebo - Weighted Mean Difference (WMD) = -0.03 (-0.09 , 0.03)

Figure 22. Cocaine – ASI Drug Composite



TOURETTE'S. We found no new clinical trials that studied atypical antipsychotics for Tourrette's syndrome published after our original CER. That CER reported risperidone was superior to placebo in one small trial, and it was at least as effective as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.

There were two observational studies[255-256] of aripiprazole that reported effectiveness data after our 2006 CER. One was a retrospective observational study for the treatment of tics with or without co-morbid explosive disorder. Thirty-seven patients, aged 8-18 years old were treated with aripiprazole 2.5-40 mg for 12 weeks. All of the 29 subjects who completed the trial experienced a reduction in their tic severity. However, eight subjects discontinued early due to inability to tolerate the medication.[255]

The other study treated 24 patients, aged 7-18 years old with a mean aripiprazole dose of 9.8mg for eight weeks. Overall, there was a 52.8% reduction in YGTSS scores and 19 of the 24 were described as "much" or "very much" improved per CGI-I. Six of the patients discontinued due to adverse effects.[256]

Table 21. Atypical antipsychotics for Tourette's syndrome

Study / Type	Patients / Age	Dosage / Duration	Measures	Effects
Budman, 2008[255]/ Retrospective observational study	37 patients (29 completed, 8 withdrew for inability to tolerate)/ 8-18 years	2.5-40mg (mean 11.69)/ 12 weeks	CGI- Tics	Reduction in tic severity in 100% of subjects
Yoo, 2007[256]/ Open-label, flexible dosing	24 patients (18 completed, 6 withdrew for adverse effects)/ 7-18 years	9.8 mg (+/- 4.8)/ 8 weeks	YGTSS, CGI-I, CGI-S, adverse effects checklist, EPS rating scale, height and weight, labs, ecg	52.8% reduction in mean YGTSS scores overall CGI-I much improved or very much improved in 19/24

Discussion

We conducted an extensive literature search, data abstraction, and meta-analyses, whenever possible, to assess the efficacy and comparative effectiveness of atypical antipsychotics for off-label indications. Since the publication of our original CER in 2006, many new high quality controlled trials have been published; we were able to add many to our prior quantitative analyses. Our results are summarized in Table 19. It is important to note that we found no trials of the three newest atypicals – asenopine, iloperidone, and paliperidone – for off-label uses.

We found that all the other atypicals (with the exception of ziprasidone, where we found no trials) had small but statistically significant effects in treating behavioral symptoms of dementia. Because of the plethora of trials, the large sample sizes enrolled in each trial (usually 300 or more), the quality of trials (mean Jadad score 3.2) and the consistency of the results, the strength of the evidence is high. However, the clinical benefits must be balanced against significant side effects and potential harms. (See results of Key Question Four, later in this report.)

A moderate level of evidence also suggests efficacy of aripiprazole, risperidone, and quetiapine as augmentation in treatment of MDD in patients who respond inadequately to SSRIs / SNRIs. There were also a few trials that found efficacy for ziprasidone and olanzapine; the strength of evidence is low for these two drugs, but this rating could change with the publication of additional successful trials. Effect sizes are considered moderate; NNTs range from three for quetiapine to nine for risperidone. There are a number of placebo controlled trials (PCTs) with large samples (at least 300 each) that found consistent results for quetiapine, aripiprazole and risperidone.

We found moderate strength evidence of efficacy of some atypicals as augmentation therapy for OCD and PTSD. Regarding OCD, quetiapine, risperidone have a moderate strength of evidence, and strength for olanzapine is low. Trials for OCD tend to be much smaller than those for dementia and depression; sample sizes ranged from 15 to 45 for the eleven trials contributing to our efficacy meta-analysis. The mean quality of trials is lower (2.2 on Jadad scale). Results are also less consistent. For example, in the only two PCTs of olanzapine, percentage of participants responding as measured by YBOCS did not differ from placebo. In contrast, a head-to-head trial (with no placebo) found no difference in efficacy between olanzapine and risperidone, a drug with moderate evidence of efficacy.

There is also moderate strength evidence of efficacy in reducing symptoms of combat-related PTSD from several small trials of risperidone. We also found two studies of olanzapine for PTSD; they reported conflicting results. No trials of other atypicals for PTSD have been published. Trials of PTSD tend to be of lower quality and smaller size than the depression augmentation and dementia trials. Mean Jadad score was 2.7; only one PTSD trial had over 40 participants. New, preferably larger trials must be conducted before the strength of evidence can be increased.

Regarding borderline personality disorder, strength of evidence of efficacy is low for all atypicals other than risperidone, where we found no trials. Olanzapine had the most trials (seven)

but results were inconsistent. Of note, however, in the olanzapine studies that showed no difference between drug and placebo groups at 12 week follow-up, both groups of patients showed improvement overall, with the treated patients showing a faster time to response.

We added eating disorders, anxiety, insomnia, and substance abuse to our 2010 research agenda. With the exception of generalized anxiety disorder, there is little scientific evidence that atypicals are useful in addressing symptoms of these conditions. We found no trials of atypicals for insomnia. Moderate evidence suggests that olanzapine, risperidone, and aripiprazole have no efficacy in substance abuse treatment, and that olanzapine treatment does not lead to weight increase in eating disorder patients, compared to placebo. No other atypicals have been studied in trials for these two off-label uses. We did find moderate evidence of efficacy of quetiapine in treating generalized anxiety disorder. There were too few trials of olanzapine, risperidone or ziprasadone for anxiety to pool; these trials had mixed results. Importantly, anxiety trials had larger samples (mean N = 122) and higher quality (mean Jadad score = 3.1) than most trials for OCD, PTSD, substance abuse, and eating disorders.

Finally, we reviewed trials of children and adolescents with Tourette's syndrome or ADHD; evidence of efficacy was low for use of atypicals for these conditions. No Tourette's trials have been published since our 2006 CER which reported that risperidone is at least as effective as pimozide or clonidine. Only one small trial has studied atypicals for ADHD in children with no major co-occurring disorders; risperidone users were more likely to respond than placebo patients.

These findings are valuable and can help psychiatrists make better clinical decisions based on the latest evidence. Findings are summarized in Table 22. The symbol "O" below indicates areas where we found no clinical trials of a particular atypical for that condition, while "-" indicates evidence of inefficacy for a condition, according to the psychometric measures our team considered most important. In summary, ziprasidone has no evidence of efficacy for any off-label use other than depression. The four other atypicals have shown efficacy in treating dementia, depression, and a few other conditions, depending on drug.

Table 22. Summary of strength of evidence of efficacy, by drug and condition

	Aripiprazole	Olanzapine	Quetiapine	Risperidone	Ziprasidone
Anxiety – generalized anxiety disorder	O	+	++	-	-
Anxiety – social phobia	O	+	-	O	O
Attention Deficit/Hyperactivity Disorder -no co-occurring disorders	O	O	O	+	O
Attention Deficit/Hyperactivity Disorder -bipolar children	-	O	O	O	O
Attention Deficit/Hyperactivity Disorder -mentally retarded children	O	O	O	+	O
Dementia overall	++	++	++	++	O
Dementia psychosis	++	+	+	++	O
Dementia agitation	++	++	+	++	O
Depression -MDD augmentation of SSRI / SNRI	++	+	++	++	+
Depression -MDD: Monotherapy	O	--	O	O	O
Eating Disorders	O	--	O	O	O
Insomnia – NO RCTS FOUND					
Obsessive Compulsive Disorder -augmentation of SSRI	O	+	++	++	-
Obsessive Compulsive Disorder -augmentation of citalopram	O	O	+	+	O
Personality Disorder -borderline	+	+-	+	O	-
Personality Disorder -schizotypal	O	O	O	+-	O
Post Traumatic Stress Disorder	O	+	O	++	O
Substance Abuse alcohol	--	-	-	O	O
Substance Abuse cocaine	O	-	O	-	O
Substance Abuse methamphetamine	-	O	O	O	O
Substance Abuse -methadone clients	O	O	O	-	O
Tourette's Syndrome	O	O	O	+	-

++: moderate or high evidence of efficacy
+ : low or very low evidence of efficacy
+- : mixed results
- : low or very low evidence of inefficacy
-- : moderate or high evidence of inefficacy
O : no trials

Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, the possibility of publication bias still exists. Table 23 below displays our assessment of heterogeneity by condition and outcome. For the most part, our assessment did not yield evidence of unexplained heterogeneity. Two exceptions include one outcome for depression and the YBOCS (percent of participants responded) outcome used in our OCD meta-analysis. In our analysis of atypicals as augmentation in treatment of major depressive disorder (MDD), possible publication bias appeared in studies reporting the percent of participants remitted according to the MADRS (Begg's p=.007, Egger's p=0.019). We conducted additional efficacy meta-analyses using HAM-D outcomes; efficacy results were similar, but no heterogeneity was detected. Thus, our confidence that some atypicals have efficacy as augmentation of SSRIs / SNRIs for depression remains. Heterogeneity was also evident in studies assessing the efficacy of atypicals for OCD (Begg's p=0.002, Egger's p=0.001). This heterogeneity was likely due to patient enrollment criteria; studies used different definitions of "refractory" and "treatment resistant." Another published meta-analysis of atypicals for OCD[176] found similar efficacy results but no heterogeneity according to statistical tests.

Table 23. Analysis of publication bias

Condition	Outcome	Begg's Test P-Value*	Egger's Test P-Value
Anxiety	HAM-A % Responded	0.452	0.468
Dementia	Total/Global Scores	0.889	0.830
Dementia	Psychosis	0.363	0.273
Dementia	Agitation	0.544	0.178
Depression	HAM-D % Remitted	0.771	0.245
Depression	HAM-D % Responded	0.174	0.150
Depression	MADRS % Remitted	0.007	0.019
Depression	MADRS % Responded	0.087	0.096
Eating Disorders	BMI	0.296	0.210
OCD	YBOCS % Responded	0.002	0.001
PTSD	CAPS	0.806	0.608
Substance Abuse	Alcohol Complete Abstinence	0.296	0.308
Substance Abuse	ASI Drug Composite	1.000	0.928

* Continuity Corrected

An important limitation common to systematic reviews is the quality of the original studies included. In order to measure the quality of clinical trials we used the Jadad scale.[19] As empirical evidence regarding other study characteristics and their relationship to bias is lacking, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. In our 2006 CER on off-label use of atypicals, we conducted a sensitivity analysis on the relationship between trial quality and effect size; the better quality trials reported an effect size 25 percent smaller than did lower quality trials. This finding increases the likelihood that a synthesis of results of all studies - whether narrative or quantitative – may produce inflated estimates of efficacy. As stated above, the higher general quality of the dementia and depression augmentation studies led to a greater strength of evidence rating for those uses.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals must be known to assess applicability. Such data were reported unevenly in the studies we reviewed. The dementia trials were most often conducted in nursing homes, hospitals, or assisted living facilities. According to our review on utilization patterns, these settings represent where atypicals are most often used in the elderly. Studies for other conditions were not particularly representative. For example, three of the four trials for ADHD were conducted in children with severe co-occurring conditions, such as bipolar disorder or mental retardation. Subjects in substance abuse trials were usually enrolled in outpatient or residential treatment programs. However, there was one trial of non-treatment seeking subjects;[233] it is unlikely that atypicals would be used without some initial detox or simultaneous treatment program.

In the studies of atypicals as augmentation for SSRI or SNRI patients with major depressive disorder (MDD) it was often unclear whether patients were simultaneously undergoing psychotherapy. One article[157] specifically stated that subjects were prohibited from initiating such therapy during the trial, but other articles were unclear on the issue. Thus, we don't know whether treatment over and above the medication influenced the study results. It is important to note that subjects in depression trials were recruited from both primary care and mental health centers, as depression patients have been increasingly treated in primary care settings.

We found only observational studies of atypicals for treatment of insomnia. Only one small study[172] included patients with insomnia as primary diagnosis. Others included patients with Parkinson's disease, MDD, polysubstance abuse withdrawal symptoms, and tamoxifen induced insomnia. Thus, the results of these studies should not be applied to the general population.

Key Question III:

What subset of the population would potentially benefit from off-label uses? Do effectiveness and harms differ by race/ethnicity, gender, and age group? By severity of condition and clinical subtype?

Key Points

There was no difference in effect by gender in one study of aripiprazole for major depressive disorder (MDD). No other studies stratified results by gender.

Atypicals may have greater efficacy in male combat veterans than in civilian women with PTSD.

There are insufficient data to make conclusions regarding differences in efficacy by patient age. Two studies of atypicals for MDD in older adults found them at least as efficacious as in studies conducted in the non-elderly.

There are insufficient data to make statements regarding treatment effects by race/ ethnicity, as no studies reported stratified results.

Differing measures of disease severity preclude overall conclusions about the effects of atypical antipsychotics by severity.

Detailed Analysis

There was only one study that conducted subgroup analysis by gender. In that trial, aripiprazole was used as an adjunct in treatment of major depressive disorder with results reported by mean change in MADRS total score. There was no statistically significant interaction effects for sex.[139]

Trials of PTSD were conducted in male and female populations. In the male trials [212, 216-217] PTSD was combat-related, while the female trials [213, 219] were conducted on civilian women whose PTSD was abuse-related. In pooled analysis of the three combat studies, mean difference in Clinician-Administered PTSD Scale (CAPS) was 7.95 (95% CI 1.06, 14.84) compared to placebo. Although we could not pool the results of the two trials in abused women, we note that the results of both trials were not statistically different from placebo.

There were no trials that stratified by race; therefore evidence about the differing benefits by race was not obtained.

Regarding age, as expected, most participants in ADHD and Tourette's trials were children or adolescents, while trials for dementia were done in the elderly. As these conditions are heterogeneous and use different measures of efficacy, it is not possible to compare efficacy by age group. There were no trials that specifically stratified effects by age; however, there were two depression trials conducted in an older population. One studied risperidone augmentation in patients >/= 55 years old.[137] The authors found a suggestion towards greater symptom resolution with risperidone (compared to placebo augmentation) but no significant difference in time to relapse. Reported side effects included headache, dizziness and dry mouth. The other trial studied quetiapine monotherapy in patients with depression >65 years old.[153]. The relative risk of remitting on the MADRS for those participants taking quetiapine compared to placebo was 2.48 (95% CI 1.70, 3.62); the relative risk of responding on the MADRS for those patients in the quetiapine arm versus the placebo arm was 2.11 (95% CI 1.63, 2.71). These estimates of effect size were larger than all other studies included in our depression meta-analyses (see Key Question 2) and the overall pooled estimates. Reported side effects included somnolence, headache, dry mouth, dizziness, fatigue, insomnia, constipation, diarrhea, nausea, weight increase, sedation, asthenia, extrapyramidal disorder, upper abdominal pain, back pain and dysgeusia.

There was insufficient data to conduct analyses by disease subtype, other than the PTSD analysis on combat versus civilian trauma noted above.

Studies differed in the psychometrics used to measure severity of illness, making comparisons across studies difficult. This may reflect the differing definition of disease severity seen clinically.

Discussion

In summary, there are insufficient data regarding efficacy, effectiveness, and harms, to determine what subset of the population would potentially benefit from off-label uses of atypical antipsychotic medications. Only one study conducted a subgroup analysis by gender; there were no studies that stratified by racial or ethnic group. Although many studies specified age in their inclusion criteria, no studies stratified results by age. Unfortunately, this limits the conclusions that can be determined.

Examination of the literature for differing effects of atypical antipsychotic medications by clinical subsets did not reveal studies reporting subgroup analyses. Our own meta-analysis found efficacy for combat-related PTSD in men but not for PTSD in civilian women. Due to the varying measures utilized in determining severity of illness, it was not possible to analyze treatment effects by severity of illness across any condition.

Overall, there are not enough data to suggest that a particular subset of the clinical populations, whether by demographic or illness characteristics, will show differing benefit in treatment with atypical antipsychotic treatment. More research in this area is needed.

Key Question IV:

What are the potential adverse effects and/or complications involved with off-label prescribing of atypical antipsychotics? How do they compare within the class and with other drugs used for the conditions?

Key Points

We found no trials or large observational studies of asenipine, iloperidone, or paliperdione for off-label uses.

Elderly patients - dementia studies. Our 2006 systematic review discussed a published meta-analysis of atypicals and death in Alzheimer's disease patients which included both published and unpublished trials. Death occurred in 3.5 percent of patients randomized to receive atypical antipsychotics compared with 2.3 percent of patients randomized to receive placebo. The difference in risk for death was small but statistically significant.

We found five large cohort studies that compared mortality in elderly patients taking atypical and conventional antipsychotics. Three of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison.

We used data from placebo controlled trials (PCTs) to conduct a meta-analysis on symptoms we categorized as cardiovascular (including "cardiovascular symptoms," "edema," and "vasodilation"). These events were reported significantly more often in patients taking olanzapine, risperidone, and aripiprazole than in those taking placebo. Quetiapine was not statistically associated with these symptoms.

We conducted a specific analysis on cerebrovascular accident (CVA); risperidone was the only drug associated with an increase. However, as mentioned in our 2006 report, an industry-sponsored analysis of five RCTs of olanzapine in elderly dementia patients found the incidence of cerebrovascular adverse events three times higher in olanzapine patients than in placebo patients.

Our meta-analysis of PCTs found olanzapine and risperidone statistically associated with increases in appetite/weight. As reported in 2006, in one large head-to-head trial (CATIE-AD) elderly patients with dementia who were treated with olanzapine, quetiapine or risperidone averaged a monthly weight gain of 1.0, 0.7 and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month.

Our meta-analysis of PCTs found olanzapine associated with anticholinergic events.

Our meta-analysis of PCTs also found that aripiprazole, olanzapine, quetiapine, and risperidone were each associated with both sedation and fatigue in dementia patients. Aripiprazole and risperidone were associated with an increase in extra-pyramidal symptoms (EPS); quetiapine was not. These findings echo those of our prior analyses and the CATIE-AD trial results. In the one PCT of olanzapine which reported EPS, subjects in the drug group were more likely to report these symptoms.

Endocrine adverse events are a new focus. Only one trial in elderly dementia patients reported these outcomes, there was no difference in diabetes onset or prolactin measures between patients taking risperidone and those taking placebo. One cohort study followed elderly patients enrolled in olanzapine trials; the authors found that the risk of diabetes was not significantly associated with antipsychotic treatment, but rather depended on having an elevated glucose at baseline.

We found no trials or large observational studies of ziprasidone for dementia in older adults; therefore, we can not make conclusions regarding safety of ziprasidone in this population.

In head-to-head trials of atypicals, olanzapine patients had higher odds of neurological symptoms, such as headaches and dizziness. There was a trend toward greater odds of sedation with olanzapine and quetiapine compared to risperidone.

We found one new trial comparing adverse events in elderly patients taking either risperidone or SSRIs for depression. There was no difference in adverse events. As reported in our 2006 evidence review, one trial of olanzapine versus benzodiazepines in 205 patients also showed no significant difference in adverse events.

Adults (Age 18 to 64) – studies of anxiety, depression, eating disorders, OCD, PTSD, personality disorders and substance abuse. The only significant difference in cardiovascular symptoms between atypicals and placebo involved blood pressure changes in patients taking quetiapine. No studies of any drug or condition reported CVA.

Our analysis of PCTs found that aripiprazole, olanzapine, quetiapine, and risperidone were each associated with increases in appetite/weight gain. Ziprasidone was not significantly associated with weight gain in two trials. We also found a recently published cohort study of depression treatment which reported risperidone, quetiapine, olanzapine, and ziprasidone, but not aripiprazole, were associated with an increase in the risk of incident hyperlipidemia. In our analysis of three quetiapine PCTs which reported abnormalities intriglycerides, they were more common in patients taking the drug than those taking placebo.

Endocrine and diabetes are a new focus. Two PCTs of olanzapine reported endocrine adverse events; patients taking the drug had increased odds. One PCT each of quetiapine, risperidone, and ziprasidone also reported these events. We were unable to conduct meta-analysis; however, the events were always more prevalent in the atypical group. Five PCTs of quetiapine reported diabetes outcomes; in our pooled analysis there was no statistical difference between patients taking quetiapine and those taking placebo. In the one PCT of olanzapine that reported diabetes outcomes, five of the 370 intervention patients became diabetic, compared to only one of the 377 patients taking placebo. In one head-to-head trial, olanzapine had a higher risk for precipitating diabetes than did risperidone. As reported in our 2006 evidence review, one large observational study reported lower odds of diabetes in risperidone subjects than in placebo.

Our analyses indicate that all atypical antipsychotics are associated with an increase in at least some symptoms categorized as neurological ("confusion," "dizziness," "headaches," "lightheadedness," "orthostatic dizziness," "seizure," and "tinnitus") when compared to placebo. All but risperidone were associated with increased fatigue; all were associated with sedation. Aripiprazole was associated with increased odds of akathisia, while the other drugs were not. Aripiprazole, quetiapine, and ziprasidone were associated with increased odds of extrapyramidal side effects (EPS).

Quetiapine patients had higher odds of decreased salvation, neurological events, sedation, and agitation, compared to risperidone patients in two head-to-head trials. Another head-to-head trial reported higher odds of weight gain with olanzapine, when compared to ziprasidone.

We found two trials of olanzapine versus a mood stabilizer. Olanzapine patients had lower odds of GI, low platelets and mania, but higher odds of weight gain, dry mouth, liver function test abnormality, EPS, and sedation. We found one small trial of quetiapine versus a mood stabilizer: quetiapine patients were less likely to experience EPS.

A handful of trials compared AEs between an atypicals and SSRIs. Although there were no differences in diabetes rates, higher rates of metabolic lab abnormalities were reported in one trial of quetiapine versus SSRI. Fatigue was more common in olanzapine, quetiapine, and ziprasidone than in SSRIs, and sedation was more common in olanzapine and quetiapine patients. Olanzapine and risperidone patients also had higher odds of cardiovascular adverse events.

Three trials of olanzapine and one of aripiprazole compared adverse events in conventional versus atypical antipsychotics. Weight gain was more common among both olanzapine and aripiprazole patients than those taking conventional antipsychotics. In one trial, olanzapine patients were less likely to observe cardiovascular symptoms, fever / infection, gastrointestinal, and musculoskeletal problems fatigue, akathisia, extrapyramidal side effects, and sedation. In the one aripiprazole trial, fewer aripiprazole patients experienced akathisia and EPS than those on conventional antipsychotics.

Children & adolescents – studies of ADHD and Tourette's syndrome. There were no trials or large cohort studies of olanzapine or quetiapine for ADHD or Tourette's syndrome in children / adolescents, nor were there any head-to-head trials of atypicals for these uses.

Maximum trial length was six weeks, and adverse events were few. Weight gain was more common in patients taking risperidone than those taking placebo in two PCTs. In one small PCT, EPS was less common in aripiprazole patients than placebo patients.

In one small PCT of ziprasidone, there were no significant differences in adverse events between groups.

In one small trial of clonidine versus risperidone there were no significant differences in adverse events between groups

In one trial of haloperidol versus risperidone; significantly more patients on the conventional antipsychotic reported sleep problems.

Detailed Analysis

One of the major rationales for preferring treatment with atypical antipsychotics over conventional antipsychotics is potentially greater safety. To assess this, we abstracted adverse event data from all RCTs of atypicals for off-label conditions, plus observational studies with more than 1,000 subjects. We conducted separate analyses for placebo comparisons, active comparisons (comparing atypical antipsychotics to acetylcholinesterase inhibitors, benzodiazepines, clonidine, conventional antipsychotics, mood-stabilizers, SRIs, and tricyclic antidepressants), head-to-head trials of atypicals, and observational studies. Of the 137 RCTs published since our 2006 CER, 122 reported adverse events. We pooled the new data with data from the 67 RCTs included in our 2006 adverse events analyses.

As in the 2006 analyses, we identified and grouped adverse events into clinically relevant categories. These categories were then pooled within three condition categories, based on patient age. Patient age was a proxy measure for the baseline likelihood of adverse events; in other words, children, adults, and older adults are expected to have different types of risks for adverse events. Thus, we analyzed studies of dementia patients separately (mean age = 81.5 years); pooled ADHD and Tourette's patients together; and pooled studies of the remaining conditions together (mean ages from 24.3 years for eating disorders to 47.4 years for depression). We did not pool different atypicals together; instead, we generated separate estimates for each of the five atypical antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone, and ziprasidone. Again, we found no trials of the three newer drugs (asensopine, iloperidone, paliperidone) for off-label uses.

The complete results of the adverse event analyses are presented in Appendix G. Number needed to harm (NNH) is presented where applicable. For many of the comparisons, the numbers of trials are few and the number of enrolled patients is small, resulting in wide 95 percent confidence intervals and the inability to draw conclusions. However, even with this limitation, many observations are worth noting.

Dementia. Data from trials: There were no trials or large observational studies of ziprasidone in dementia; thus, we have no data on ziprasidone's safety in the elderly.

In 2005, the FDA issued a Public Health Advisory for treatment of dementia with atypical antipsychotics after studies reported increased risk of death compared with placebo. Our 2006 CER discusses a published meta-analysis of atypical antipsychotic medication use and death in Alzheimer's disease patients which included both published and unpublished trials. Fifteen RCTs were included (eight were cited only as abstracts): four trials of risperidone, five of olanzapine, three of quetiapine, and two trials of aripiprazole. In all, 3,353 patients received an atypical antipsychotic, and 1,757 received placebo. With one exception, trials lasted from 6-12 weeks. (The one exception was 26 weeks.) Death occurred in 118 or 3.5 percent of patients randomized to receive atypical antipsychotics versus 40 or 2.3 percent of patients randomized to receive placebo. The odds ratio for death using a fixed effects model was 1.54, with a 95% confidence interval of 1.06 to 2.23. The difference in risk for death was small but statistically significant ($p = .01$). In other words, the number needed to harm was 100, although the 95% confidence

intervals were broad. Pooled data from two trials containing a haloperidol treatment arm indicated that treatment with this conventional antipsychotic was also associated with a similar, albeit not statistically significant, increase in death. The authors concluded that atypical antipsychotic drugs may be associated with a small increased risk for death compared with placebo. As this meta-analysis was well-conducted and included more trials that were available to us, we did not conduct our own meta-analysis of mortality and atypical antipsychotic use for dementia.

In this update, we conducted a meta-analysis on the group of symptoms we categorized as cardiovascular (including "cardiovascular symptoms," "edema," and "vasodilation"). They were reported significantly more often in patients taking aripiprazole, olanzapine, and risperidone than in those taking placebo (OR of 2.20, 2.33, and 2.08, respectively). The number needed to harm (see Table 24) was 16 for aripiprazole, 32 for olanzapine and 29 for risperidone. Quetiapine was not statistically associated with these symptoms. We conducted a specific analysis on cerebrovascular accident (CVA); risperidone was the only drug associated with an increase. The pooled odds ratio was 3.12 (95% CI 1.32, 8.21); number needed to harm was 89.

Table 24. Cardiovascular adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	**Drug**	**# of studies**	**# adverse events**	**sample size**	**# adverse events**	**sample size**	**Pooled OR**	**95% CI**	**NNH**	**95% CI NNH**
Cardiovascular/ CVA	Olanzapine	2	4	232	6	278	1.46	0.33, 7.44	NC	NC
Cardiovascular/ CVA	Risperidone	4	8	753	24	1099	3.12	1.32, 8.21	89	44, NC
Cardiovascular/ CVA	Aripiprazole	3	2	253	2	340	0.70	0.05, 10.48	NC	NC
Cardiovascular/ CVA	Quetiapine	3	6	241	3	185	0.65	0.10, 3.08	NC	NC
Cardiovascular – other	Olanzapine	5	9	440	40	778	2.33	1.08, 5.61	32	19, 95
Cardiovascular – other	Risperidone	6	34	1010	119	1757	2.08	1.38, 3.22	29	20, 56
Cardiovascular – other	Aripiprazole	2	22	242	74	488	2.20	1.27, 3.96	16	9, 80
Cardiovascular – other	Quetiapine	3	15	254	29	355	1.08	0.53, 2.30	NC	NC

NC = Not calculated

In the PCTs, olanzapine and risperidone were statistically associated with increases in appetite/weight (OR 4.69, 95% CI 1.87, 14.14, NNH = 19; OR 3.40, 95% CI 1.08, 12.75, NNH=35; respectively) while only olanzapine was associated with anticholinergic events (OR 3.29, 95% CI 1.62, 7.17, NNH = 5). As reported in our 2006 evidence report, the CATIE-AD trial found that patients with dementia who were treated with olanzapine, quetiapine or risperidone averaged a monthly weight gain of 1.0, 0.7 and 0.4 pounds while on treatment, compared to a weight loss among placebo-treated patients of 0.9 pounds per month.

Table 25, below, displays our current analyses on neurological side effects. Aripiprazole, olanzapine, quetiapine, and risperidone were each associated with sedation in dementia patients. The NNH ranged from 7 to 10. Each of these drugs was also statistically associated with an increase in fatigue; NNH ranged from 18 to 21 (not shown). To analyze extrapyramidal side effects (EPS), we were able to pool five PCTs of aripiprazole, five PCTs of risperidone, and three of quetiapine. Aripiprazole and risperidone were associated with an increase in EPS (OR 2.02 and 3.00 respectively) compared to placebo; quetiapine was not. The NNH for aripiprazole was 32 and 20 for risperidone. In the one PCT of olanzapine which reported EPS, subjects in the drug group were more likely to report these symptoms, odds ratio of 15.21, NNH=6).

Table 25. Neurological adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	**Drug**	**# of studies**	**# adverse events**	**sample size**	**# adverse events**	**sample size**	**Pooled OR**	**95% CI**	**NNH**	**95% CI NNH**
Neuro/Movement Disorder/EPS	Aripiprazole	5	23	499	46	593	2.02	1.17, 3.59	32	17, 317
Neuro/Movement Disorder/EPS	Olanzapine	1	2	142	18	100	15.21	3.50, 138.55	6	4, 11
Neuro/Movement Disorder/EPS	Quetiapine	3	9	254	18	355	1.15	0.46, 3.08	NC	NC
Neuro/Movement Disorder/EPS	Risperidone	5	31	916	130	1561	3.00	1.96, 4.70	20	15, 32
Neuro/Movement Disorder/Gait	Olanzapine	4	15	373	79	641	2.75	1.52, 5.79	12	9, 20
Neuro/Movement Disorder/Gait	Aripiprazole	1	1	121	16	366	5.47	0.83, 231.93	NC	NC
Neuro/Movement Disorder/Gait	Quetiapine	3	6	333	18	426	2.36	0.85, 7.59	NC	NC
Neuro/Movement Disorder/Gait	Risperidone	3	8	406	32	448	3.04	1.32, 7.84	19	13, 41

NC = Not Calculated

Our expert panel reported cases of diabetes onset in elderly patients taking atypicals; thus, we were encouraged to conduct an analysis on endocrine outcomes. Only one trial, of risperidone, reported this category of adverse events; there was no difference between patients taking the drug and those taking placebo, although the confidence intervals are wide. Results are displayed in Table 26 below.

Table 26. Endocrine adverse events among dementia patients – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Diabetes	Risperidone	1	5	238	4	235	0.81	0.16, 3.80	NC	NC
Prolactin	Risperidone	1	0	238	0	235	NC	NC	NC	NC

NC = Not Calculated

As displayed in Table 27, urinary symptoms were significantly more common in dementia patients treated with aripiprazole, olanzapine, quetiapine, and risperidone than with placebo; NNH ranged from 8 to 21. Confidence intervals were very wide.

Table 27. Urinary symptoms among dementia patients – Atypical Antipsychotics Compared to Placebo

		Placebo		Intervention Groups					
Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Aripiprazole	5	77	594	221	856	2.72	1.98, 3.79	8	6, 11
Olanzapine	1	1	94	19	204	9.51	1.47, 401.07	12	8, 27
Quetiapine	2	12	191	44	332	2.37	1.16, 5.15	14	8, 51
Risperidone	4	71	665	164	1060	1.55	1.13, 2.13	21	13, 63

We found six head-to-head trials of atypicals for dementia which reported adverse events, including the CATIE-AD trial mentioned earlier. Subjects taking olanzapine had greater odds of having a neurological symptom such as “confusion,” “dizziness,” “headaches,” “lightheadedness,” “orthostatic dizziness,” “seizure,” or “tinnitus” than those taking risperidone (OR 1.54, 95% CI 1.02, 2.34). There also was a trend toward greater odds of sedation with olanzapine (OR 1.40, 95% CI 0.96, 2.05) and quetiapine (OR 1.93, 95% CI 0.97, 3.97) than risperidone, but the results do not meet traditional levels of statistical significance. In one head-to-head trial, a risperidone subject reported a pulmonary adverse event, compared with no subjects in the olanzapine group. In one trial of risperidone versus quetiapine, five of the 34 risperidone subjects reported musculoskeletal problems, compared to none of the 38 placebo patients.

We found one new trial comparing adverse events in elderly patients taking either risperidone or SSRIs for depression. There was no difference in adverse events. As reported in our 2006 evidence review, one trial of olanzapine versus benzodiazepines in 205 patients also showed no significant difference in adverse events.

Data from cohort studies: There were also nine large cohort studies that reported adverse effects occurring within elderly population taking atypicals for symptoms of dementia; they are displayed in Table 28. Five examined mortality. Populations ranged in size from 9,700 to over 90,000. All were conducted in the U.S. or Canada. The first found an increased risk of death with

atypical antipsychotic use, compared to not using antipsychotics. However, the risk of death with conventional antipsychotics was greater than that with atypicals.[63] Another study found that patients taking atypicals had a similar adjusted mortality risk to those taking conventional antipsychotics. Both types of antipsychotics had a higher mortality risk than that associated with taking a non-antipsychotic medication.[257] A study looking specifically at sudden cardiac death found that users of either conventional or atypical antipsychotic medications had a similar, dose-related increase in sudden cardiac death.[258] These findings echo another study that found the greatest increase in mortality occurring in those who took higher than the median dose. However, in this study, the dosage risk was for conventional antipsychotic therapy. The authors found that the risk of death was higher with conventional versus atypical antipsychotics and the highest risk was during the first 40 days after starting the drug therapy.[62] Another study followed new users of antipsychotic medications in nursing home residents[259] over six months. A higher rate of death was found for users of conventional antipsychotics compared to users of atypicals.

Table 28. Adverse events in large observational studies

Reference	Sample	Treatment	Outcomes Measured	Findings
Gill,2007[63]	n= 27,259 propensity score-matched pairs Ontario, Canada residents >66 yo dementia per Ontario Health Insurance Plan or Discharge Abstract Database 4/1/97-3/31/02. Community dwelling and long-term care	New users of antipsychotics per Ontario Drug Benefit program after cohort entry atypicals: olanzapine, quetiapine, risperidone Or conventional agents	All-cause mortality as recorded in the Registered Persons Database or the Discharge Abstract Database	New use of atypical antipsychotic associated with statistically significant increase in the risk of death compared with nonuse (community dwelling-adjusted hazard ratio, 1.31 [95% CI, 1.02-1.7]; absolute risk difference 0.2 percentage point. Long-term care 1.55 [CI, 1.15-2.07]; 1.2 percentage points) Conventional antipsychotic use associated with higher risk of death than use of atypicals
Kales,2007[257]	n= 10,615 patients US residents >65 yo dementia per Department of Veteran Affairs national data 2001-2005 outpatient	New users of psychiatric medication after cohort entry atypicals: aripiprazole, clozapine, quetiapine, risperidone, ziprasidone Or conventional agents	12 month mortality rates	Higher mortality rates in users of antipsychotics than nonantipsychotics (22.6-29.1% vs 14.6%) No significant difference in mortality rates between users of atypical vs conventional antipsychotics
Ray,2009[258]	n= 90,307 users of antipsychotics vs 186,000 matched nonusers 30-74 yo Medicaid enrollees in Tennessee 1/1/90-12/31/05	clozapine, quetiapine, olanzapine, risperidone Or conventional agents	Sudden cardiac death (computerized death certificates linked to computerized Medicaid records)	Higher rates of sudden cardiac death in users of antipsychotics- 1.99 (95% CI, 1.68-2.34) than nonusers- 2.26 (95% CI, 1.88-2.72). Incidence-rate ratio for users of atypicals vs conventionals was 1.14 (95% CI,0.93-1.39) For both classes, risk increased with increasing dose

Reference	Sample	Treatment	Outcomes Measured	Findings
Schneeweiss,2007[62]	n= 37,241 users of antipsychotics >65 yo British Columbia Ministry of Health data 1/1/96- 12/31/04	Per PharmaNet Database risperidone, quetiapine, olanzapine, clozapine Or conventional agents	All-cause mortality per BC Vital Statistics Agency	Risk of death was comparable and possibly greater with conventional (14.1% died) compared to atypical agents (9.6% died). Mortality ratio 1.47, 95% CI 1.39-1.56
Liperoti,2009[259]	n= 9,729 new users of antipsychotics In Medicare or Medicaid certified nursing homes in Kansas, Maine, Mississippi, Ohio, South Dakota >65 yo with dementia Data per Systematic Assessment of Geriatric drug use via epidemiology (SAGE) 1998-2000	risperidone, olanzapine, quetiapine, clozapine Or conventional agents	All-cause mortality	Higher rate of death in users of conventional vs atypical agents (hazard ratio 1.26; 95% CI, 1.13-1.42)
Micca 2006[260]	n= 1,398 >65 yo with dementia Data per olanzapine clinical trial database	olanzapine	Treatment-emergent diabetes (TED): defined as 2 casual glucose values >200mg/dL at any time after baseline or 1 casual glucose >200mg/dL at the final visit, initiation of antidiabetic medication or new clinical diagnosis of diabetes.	Antipsychotic treatment was not significantly associated with increased risk of TED (HR=1.36)

Reference	Sample	Treatment	Outcomes Measured	Findings
Lipkovich,2007[261]	n= 1,267 >65 yo with dementia and behavioral disturbances Data per olanzapine clinical trial database	olanzapine	Weight change patterns after 20 weeks of treatment	Estimated probability of gaining more than 7% of initial body weight was significantly greater with olanzapine vs placebo (P< .001)
Barnett,2007[262]	n= 14,029 >65 yo with dementia Data per Veterans Administration and Medicare databases Followed 18 months (2002-2003)	olanzapine, risperidone, quetiapine	Inpatient admission with a primary or principal diagnosis of cerebrovascular event (CVE) as identified by ICD-9-CM codes from administrative data	CVE risk did not differ in users of atypicals, conventionals or no antipsychotic
Rochon,2008[263]	n= 20,682 community dwelling and 20,559 nursing home dwelling >66yo with dementia Data per Ontario, Canada administrative health care data 30 day f/u between 4/1/97-3/31/04	olanzapine, quetiapine, risperidone Or conventional agents Or neither	Any serious adverse event as defined by the International Conference on Harmonization Clinical Safety Data Management: Definitions and Standards for Expedited Reporting guidelines (ie-results in death, is life-threatening, requires inpatient hospital admission or prolongation of existing hospital stay, or results in persistent or significant disability/incapacity	Users of atypicals were 3.2 times more likely (95% CI, 2.77-3.68) to develop a serious adverse event whereas users of conventionals were 3.8 times more likely (95% CI, 3.31-4.39)

Other cohort studies focused on diabetes, weight gain, cerebrovascular events and any serious event, in general. Regarding diabetes, one industry-sponsored and conducted study focused specifically on elderly subjects enrolled in olanzapine trials and found that the risk of diabetes was elevated (hazard ratio = 1.36) but this association was not statistically significant. These authors concluded that the risk of diabetes was more dependent on having an elevated glucose at baseline.[260]

A cohort study of mostly underweight or normal weight patients with dementia found a greater probability of gaining weight with olanzapine versus other agents, particularly if their BMI was less than 25 at baseline.[261]

A large study evaluating information from the Veterans Administration and Medicare databases observed patients with dementia who used antipsychotics over an 18 month period. They found no difference between risk of cerebrovascular event by whether the patient used a conventional, atypical, or no antipsychotic therapy. The only altered risk was in patients with the vascular dementia subtype who received risperidone. They had a decreased risk of cerebrovascular event compared to haloperidol, whereas olanzapine and quetiapine did not.[262]

One study examined serious adverse events among older adults with dementia living in the community versus in a nursing home. Researchers monitored for any event that resulted in death, was life threatening, required an inpatient hospital admission or prolongation of an existing hospital stay or resulted in persistent or significant disability incapacity. Patients receiving either an atypical or conventional antipsychotic agent were more than three times more likely to develop a serious event during the 30 days of follow-up. [263]

Children/adolescents with ADHD or Tourette's syndrome. Our 2006 CER did not include studies of ADHD. Instead, our 2006 analyses of adverse events in children and adolescents included studies of Tourette's syndrome and autism. Autism is beyond the scope of the current report; thus, those trials are not included in the current analysis.

Data from trials: Our adverse events analyses for Tourette's syndrome and ADHD patients included four PCTs. There were no trials of olanzapine or quetiapine in this population, nor were there any head-to-head trials of atypicals.

Results showed several differences between atypical antipsychotics and placebo. In two trials of risperidone, no placebo patients gained weight, compared to eight of 28 patients on the drug. In another small trial, 32.0% of patients on aripriprazole reported EPS, compared to 83.3% of placebo patients. The one PCT of ziprasidone had only 28 patients; there were no significant difference in adverse events between groups. Of note, these trials were in general of modest duration, from four to six weeks.

We found one small trial of clonidine versus risperidone; there were no significant differences in adverse events. We also found one trial of haloperidol versus risperidone; seven of the 24 patients on the conventional antipsychotic reported sleep problems, compared to only one of the 26 patients on risperidone.

Data from cohort studies: We did not identify any cohorts of sample sizes of 1000 patients or greater for the conditions of ADHD or Tourette's syndrome.

Other conditions. Data from trials: Our final adverse events analysis combined trials for anxiety, eating disorders, depression, OCD, PTSD, personality disorders, insomnia, and substance abuse. As displayed in Table 29, in the PCTs, aripiprazole, olanzapine, quetiapine, and risperidone were each statistically associated with increases in appetite/weight gain (OR 4.18, 11.30, 2.66, and 3.78, respectively) compared to placebo, with olanzapine having the largest association by more than a factor of two. Ziprasidone was not significantly associated with weight gain in two trials.

Table 29. Appetite or weight increase in other conditions – Atypical Antipsychotics Compared to Placebo

		Placebo		Intervention Groups					
Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Aripiprazole	4	8	686	35	701	4.18	1.88, 10.56	26	18, 49
Olanzapine	11	103	819	382	818	11.30	8.22, 15.74	3	3, 3
Quetiapine	12	86	1690	265	2733	2.66	2.01, 3.54	22	16, 32
Risperidone	4	5	197	24	237	3.78	1.35, 13.09	13	8, 32
Ziprasidone	2	2	113	5	251	1.24	0.19, 13.59	NC	NC

NC = Not Calculated

Death was reported only in two trials of quetiapine; there was no difference between drug and placebo groups. No studies reported CVA. The only significant difference in cardiovascular symptoms between atypicals and placebo involved blood pressure changes in patients taking quetiapine. Strangely, the drug was associated with both decrease (OR 2.09, 95% CI 1.29, 3.44) and increase (OR 1.71, 95% CI 1.22, 2.39) in blood pressure, casting doubt on this being a causal relationship.

As displayed in Table 30 below, we conducted a meta-analysis on metabolic outcomes, as experts informed us of recent reports of increases in diabetes rates among some patients taking certain atypicals. Results should be interpreted with caution, as we found only one study each of quetiapine, risperidone, and ziprasidone that reported endocrine abnormalities. The risperidone and ziprasidone groups were very small, and only one or two subjects, respectively, had endocrine abnormalities, as compared to no one in either placebo group. "Endocrine abnormalities" in this analysis were a collection of endocrine events other than diabetes (which is reported separately in Table 27), including laboratory abnormalities such as hyperprolactinemia, elevated thyroid stimulating hormone levels, and hypothyroidism, as well as clinical findings commonly due to endocrine abnormalities, such as gynecomastia and amenorrhea. Regarding quetiapine, five of the 298 subjects had endocrine adverse events, compared to only one of 148 subjects in the placebo group. In two PCTs of olanzapine, the drug was significantly associated with endocrine adverse events (OR 2.37, 95% CI 1.18, 4.94).

Five PCTs of quetiapine reported diabetes outcomes; the pooled odds ratio was elevated at 1.40 but this was not statistically significant compared to placebo. In the one PCT of olanzapine that reported diabetes, five of the 370 intervention patients became diabetic, compared to only

one of the 377 patients taking placebo, an odds ratio of 5.14, but this was not statistically significant, with very wide confidence intervals (0.6 to 244). In our analysis of three quetiapine PCTs which reported metabolic lab abnormalities (clinically important increases in triglycerides), they were more common in patients taking the drug than those taking placebo (OR 2.20, 95% CI 1.43, 3.47).

Table 30. Endocrine and other metabolic lab abnormalities in other conditions – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Endocrine	Olanzapine	2	15	190	31	184	2.37	1.18, 4.94	11	6, 43
Endocrine	Quetiapine	1	1	148	5	298	2.50	0.28, 119.45	NC	NC
Endocrine	Risperidone	1	0	12	1	19	NA	NA	NC	NC
Endocrine	Ziprasidone	1	0	30	2	30	NA	NA	NC	NC
Diabetes	Olanzapine	1	1	377	5	370	5.14	0.57, 244.28	NC	NC
Diabetes	Quetiapine	5	11	857	31	1537	1.40	0.68, 3.12	NC	NC
Prolactin	Risperidone	1	0	10	1	15	NA	NA	NC	NC
Metabolic lab abnormality	Quetiapine	3	32	537	108	903	2.20	1.43, 3.47	17	11, 32

NC = Not Calculated

As displayed in Table 31, all atypical antipsychotics were associated with an increase in at least some symptoms categorized as neurological ("confusion," "dizziness," "headaches," "lightheadedness," "orthostatic dizziness," "seizure," and "tinnitus") when compared to placebo. All drugs but risperidone were statistically associated with increased fatigue compared to placebo. NNH ranged from 14 to 19. Aripiprazole was associated with increased odds of akathisia (OR 11.78, 95% CI 7.40, 19.61), while the other drugs were not. Aripiprazole, quetiapine, and ziprasidone were associated with increased odds of extrapyramidal side effects (EBS). NNH was 11 for aripiprazole and 20 for both quetiapine and ziprasidone. All atypicals were associated with increased odds of sedation. NNH ranged from three for quetiapine to 13 for risperidone.

Table 31. Neurological adverse events in other conditions – Atypical Antipsychotics Compared to Placebo

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
Fatigue	Aripiprazole	4	31	686	82	701	2.86	1.83, 4.55	14	10, 23
Fatigue	Olanzapine	7	43	737	80	720	2.06	1.37, 3.12	19	12, 41
Fatigue	Quetiapine	11	73	1638	279	2702	2.82	2.10, 3.82	17	14, 23
Fatigue	Risperidone	4	9	233	9	274	0.83	0.28, 2.41	NC	NC
Fatigue	Ziprasidone	2	0	69	8	111	NA	NA	14	8, 42
Akathisia	Aripiprazole	5	24	769	190	779	11.78	7.40, 19.61	5	4, 6
Akathisia	Olanzapine	1	7	25	9	23	2.04	0.50, 8.92	NC	NC
Akathisia	Quetiapine	4	5	488	10	632	1.31	0.38, 5.07	NC	NC
Akathisia	Risperidone	1	0	18	1	19	NA	NA	NC	NC
Akathisia	Ziprasidone	3	9	161	36	321	2.11	0.96, 5.15	NC	NC

			Placebo		Intervention Groups					
Adverse Events	Drug	# of studies	# adverse events	sample size	# adverse events	sample size	Pooled OR	95% CI	NNH	95% CI NNH
EPS	Aripiprazole	5	43	605	99	610	2.75	1.83, 4.19	11	8, 18
EPS	Olanzapine	3	18	65	17	71	0.87	0.25, 2.97	NC	NC
EPS	Quetiapine	5	32	731	104	1110	2.54	1.63, 4.03	20	14, 37
EPS	Risperidone	1	1	10	0	15	0.00	0.00, 26.00	NC	NC
EPS	Ziprasidone	3	6	161	28	321	3.12	1.15, 10.62	20	11, 135
Sedation	Aripiprazole	7	73	810	160	820	3.03	2.15, 4.32	10	7, 14
Sedation	Olanzapine	14	127	904	279	901	2.95	2.29, 3.82	6	5, 8
Sedation	Quetiapine	15	345	1899	1517	3135	4.73	4.07, 5.51	3	3, 4
Sedation	Risperidone	8	25	290	54	336	2.43	1.39, 4.34	13	8, 42
Sedation	Ziprasidone	5	21	212	95	392	3.90	2.15, 7.44	7	5, 12

NC = Not Calculated

Patients taking atypicals other than aripiprazole had greater odds of decreased salivation (dry mouth) than patients taking placebo. NNH ranged from five for olanzapine to 19 for ziprasidone (not shown).

Regarding adults aged 18 to 65, we found one head-to-head trial of olanzapine versus ziprasidone and two head-to-head trials comparing quetiapine to risperidone. Olanzapine was associated with higher odds of weight gain (OR 4.02, 95% CI 2.25, 7.48) when compared to ziprasidone. When compared with risperidone, quetiapine had higher odds of decreased salivation, neurological events, sedation, and agitation.

There were two trials of olanzapine versus a mood stabilizer. Olanzapine patients had lower odds of gastrointestinal side effects, low platelet count and mania. Olanzapine patients had higher odds of weight gain, dry mouth, liver function test abnormality, EPS, sedation, speech disorder, and depression. We found one small trial of quetiapine versus a mood stabilizer: the only difference in AEs involved EPS, with quetiapine patients less likely to experience them.

A handful of trials compared AEs between an atypical antipsychotic arm and an SSRI arm. Olanzapine and quetiapine patients had greater odds of weight gain than placebo patients, while risperidone patients did not. Olanzapine and risperidone patients also had higher odds of cardiac events. Olanzapine, quetiapine and ziprasidone patients had higher odds of dry mouth, while risperidone patients did not. Although there was no difference in diabetes rates, higher rates of metabolic lab abnormalities were reported in one trial of quetiapine versus SSRI. Fatigue was more common in olanzapine, quetiapine, and ziprasidone than in SSRIs, and sedation was more common in olanzapine and quetiapine patients.

We were able to compare adverse events in conventional versus atypical antipsychotics in three trials of olanzapine and one of aripiprazole. Weight gain was more common among both olanzapine and aripiprazole patients than those taking conventional antipsychotics (OR 2.65 and 1.61 respectively). In one trial, olanzapine patients were less likely to observe cardiovascular symptoms, fever / infection, gastrointestinal, and musculoskeletal problems. Olanzapine patients were also less likely to experience the neurological symptoms fatigue, akathisia, extrapyramidal side effects, and sedation in this study. In one trial of aripiprazole versus conventional

antipsychotics, fewer aripiprazole patients experienced akathisia (OR 0.44, 95% CI 0.33, 0.60) and extrapyramidal side effects (OR 0.24,95% CI 0.18, 0.32).

Schizophrenia. Because of the paucity of data directly comparing adverse events among atypical antipsychotics prescribed for off-label uses outside of dementia, we reviewed the results of the CATIE trial, a multi-center study at 57 US sites that randomized 1,493 patients with chronic schizophrenia (the indicated condition for these drugs) to receive either olanzapine, quetiapine, risperidone, ziprasidone, or the conventional antipsychotic, perphenazine. This study found that risperidone had the lowest rate of treatment discontinuation due to intolerable side effects (10 percent), whereas olanzapine had the highest rate (18 percent). More patients treated with perphenazine discontinued treatment due to extrapyramidal effects than did those treated with any of the atypical antipsychotics (8 percent vs. 2-4 percent). However, there were no significant differences among the groups in the incidence of extrapyramidal side effects, akathisia, or movement disorders, as measured by the AIMS Global Severity Score, the Barnes Akathisia Rating Scale, or the Simpson-Angus Extrapyramidal Signs Scale. Weight gain was more common in patients treated with olanzapine (average weight gain of two lbs. per month) than in other patients. Two to three times as many patients in the olanzapine-treated group gained 7 percent or more of their baseline body weight as in the other groups. More patients discontinued therapy with olanzapine due to weight gain or metabolic effects than those treated with other drugs (9 percent vs. 1-4 percent). Adverse changes in glycosylated hemoglobin, cholesterol, and triglycerides were also more likely in olanzapine-treated patients than in those treated with the other drugs, while changes in blood glucose level were also greater in olanzapine-treated patients, but the difference did not reach statistical significance. Only risperidone was associated with increasing prolactin levels. Quetiapine treated patients had higher rates of anticholinergic effects (such as dry mouth) than the other drugs, whereas patients treated with olanzapine or quetiapine had lower rates of insomnia than did patients in the other groups. Although the CATIE trial has been critiqued for the dropout rate and the perception that the dose of olanzapine used was comparatively higher than the dose for the other atypical antipsychotics, these data support the findings from the clinical trials of atypical antipsychotics for off-label indications that olanzapine causes the most weight gain but is associated with lower rates of insomnia and that treatment with atypical antipsychotics results in fewer extrapyramidal side effects and movement disorders than does treatment with conventional antipsychotics.

Data from cohort studies: As reported in our original evidence report, one large observational study reported lower odds of diabetes in risperidone subjects than in placebo subjects (OR= 0.21, 95% CI 0.07, 0.51).

There was one new cohort study that looked at the risk of hyperlipidemia with antipsychotic treatment of depression. Treatment with risperidone, quetiapine, olanzapine and ziprasidone, but not aripiprazole, caused a significant increase in the risk of incident hyperlipidemia.[264]

Discussion

In summary, there is consistent high strength evidence across multiple trials that olanzapine is associated with more weight gain than placebo, typical antipsychotics, or other atypical antipsychotics. This was a conclusion from our 2006 report; that conclusion is unchanged in this update. Evidence about weight gain for other atypical antipsychotics is not as robust, but stronger in this update than in our earlier report. In non-elderly adults, risperidone, quetiapine and aripiprazole are all statistically significantly associated with weight gain compared to placebo. From limited data ziprasidone was not associated with weight gain.

There is an emerging signal that some atypical antipsychotics are associated with the development of metabolic laboratory abnormalities or overt diabetes. Again, olanzapine stands out from the other drugs with regard to this signal. The strength of evidence for this signal is low, meaning we expect further research to change our confidence in the estimate of the effect and is likely to change the effect.

Although the evidence from off-label use is insufficient to draw conclusions, limited evidence from patients with schizophrenia suggests that atypical antipyschotics are associated with less tardive dyskinesia than are high doses of haloperidol. The strength of evidence for this outcome is low. There is moderate to high evidence that most atypical antipsychotics for whom data are available are associated with an increase in extrapyramidal signs or symptoms (excluding tardive dyskinesia) relative to placebo. The CATIE-AD trial concluded that EPS are more common with olanzapine and risperidone that quetiapine. There is also low-strength evidence that, in adults, the atypical antipsychotics aripiprazole and olanzapine are associated with a lower risk of side effects than are conventional antipsychotics.

There is high strength evidence from meta-analyses that the use of atypical antipsychotics is associated with an increased risk of death in elderly patients with dementia and agitation. For risperidone, this outcome may be related to an increased risk of stroke. New since our prior report is stronger evidence that conventional antipsychotics probably also increase the risk of death in similar patients, perhaps to the same or greater degree than atypical antipsychotics; however, the strength of evidence for this outcome is moderate, as data come primarily from observational studies. Further research may change our confidence in the estimate and may change this estimate.

Other differences in adverse events/safety between atypical antipsychotics and conventional antipsychotics or placebo were either small or inconsistent. New since our prior report is one exception to this general conclusion: an emerging signal of an increase in urinary symptoms in older adults with dementia taking atypical antipsychotics, relative to placebo.

Key Question V:

What is the effective dose and time limit for off-label indications?

Key Points

Dementia trials that included arms with different dosages usually reported a dose-response trend with higher doses resulting in higher efficacy; this trend was not statistically significant.

Our meta-analyses of MDD SSRI augmentation trials that compared quetiapine dosages found no statistical difference between 150 mg and 300 mg in percent of sample remitting or responding based on the MADRS.

One trial of the treatment of borderline personality disorder with olanzapine demonstrated improvement when 5-10 mg daily was used but no difference from placebo with 2.5 mg dose.

Our meta-analysis of olanzapine for eating disorders found no increase in BMI compared to placebo at either one or three months.

Our meta-analysis of PTSD trials found pooled results from at least 12 weeks follow-up were not statistically different from those reported at less than 12 weeks.

Detailed Analysis

Dosage. Five of the dementia PCTs contained treatment arms for different doses. There were too few studies to pool dosage results by drug: we found one of aripiprazole,[97] two of olanzapine,[121, 124] one of quetiapine,[103] and one of risperidone.[128] Each of these studies reported results per arm for total score agitation scale, and psychosis scales on the BEHAVE-AD, BPRS, or NPI. The results of these trials are displayed on Figures 23, 24, and 25. All but one study of olanzapine[124] reported increased efficacy with increased dosage. However, this trend is not statistically significant, as the 95% confidence intervals for the treatment arms in each study overlap.

Figure 23. Dementia PCTs – with dose comparisons – Total/global scores

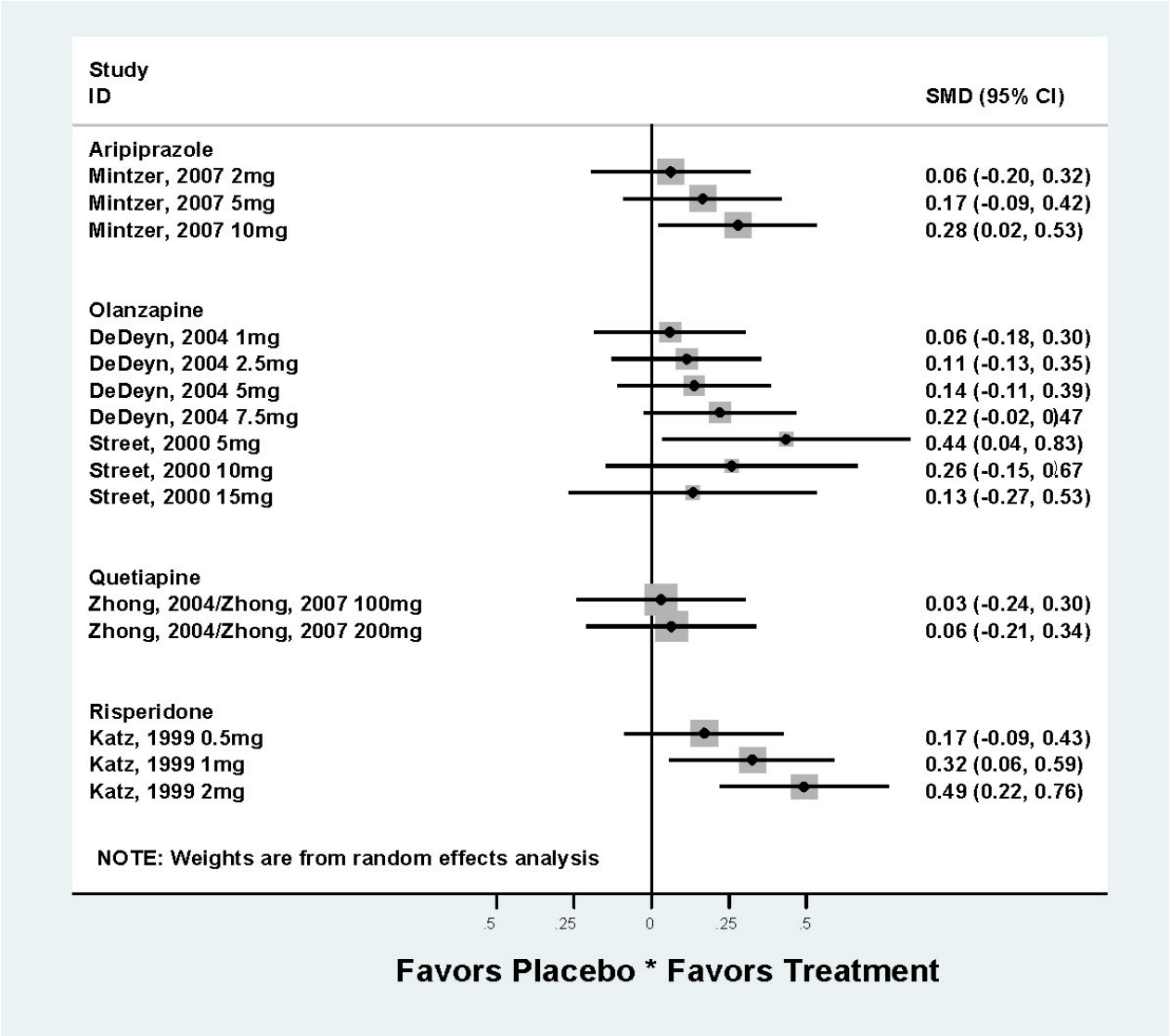


Figure 24. Dementia: PCTs with dose comparisons - Psychosis

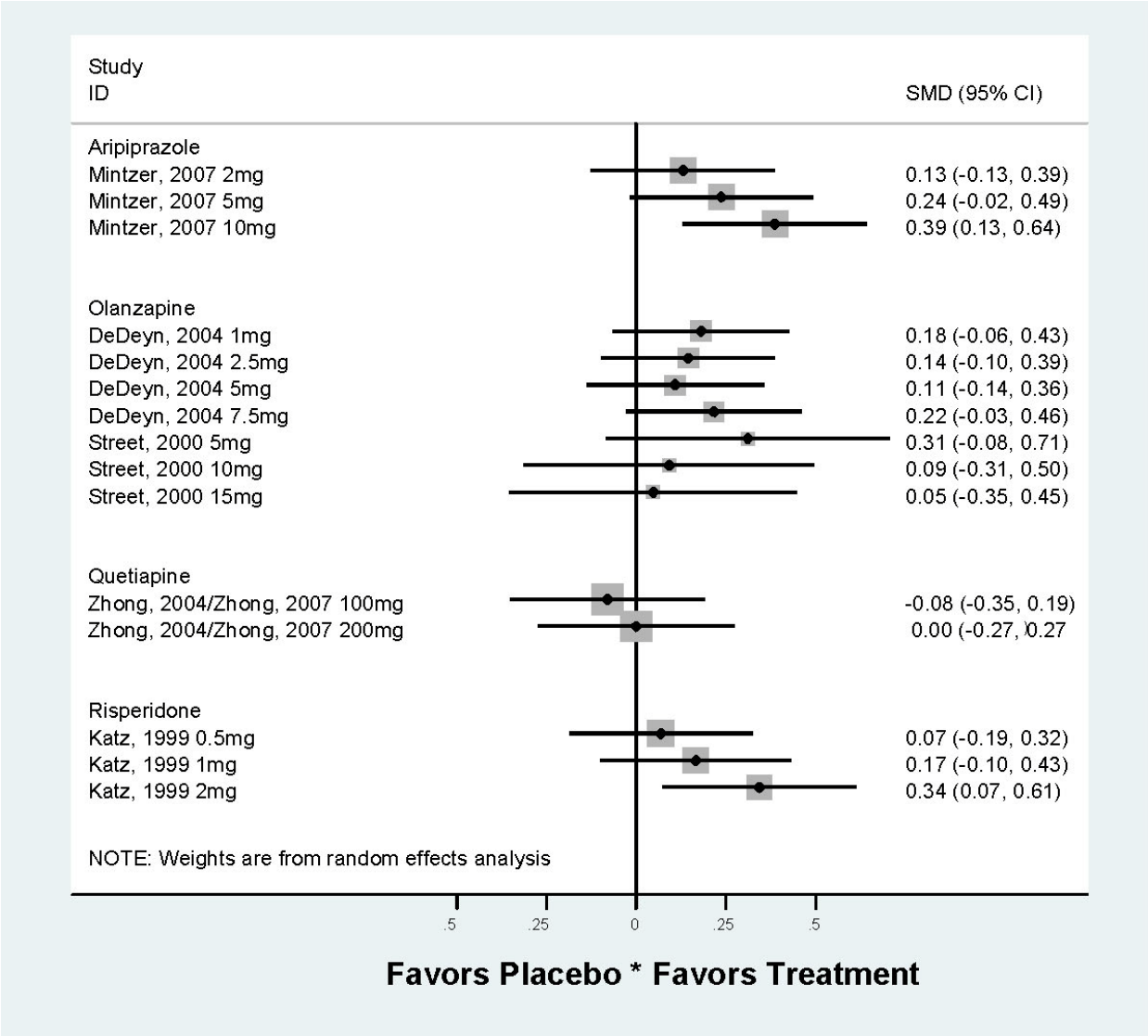
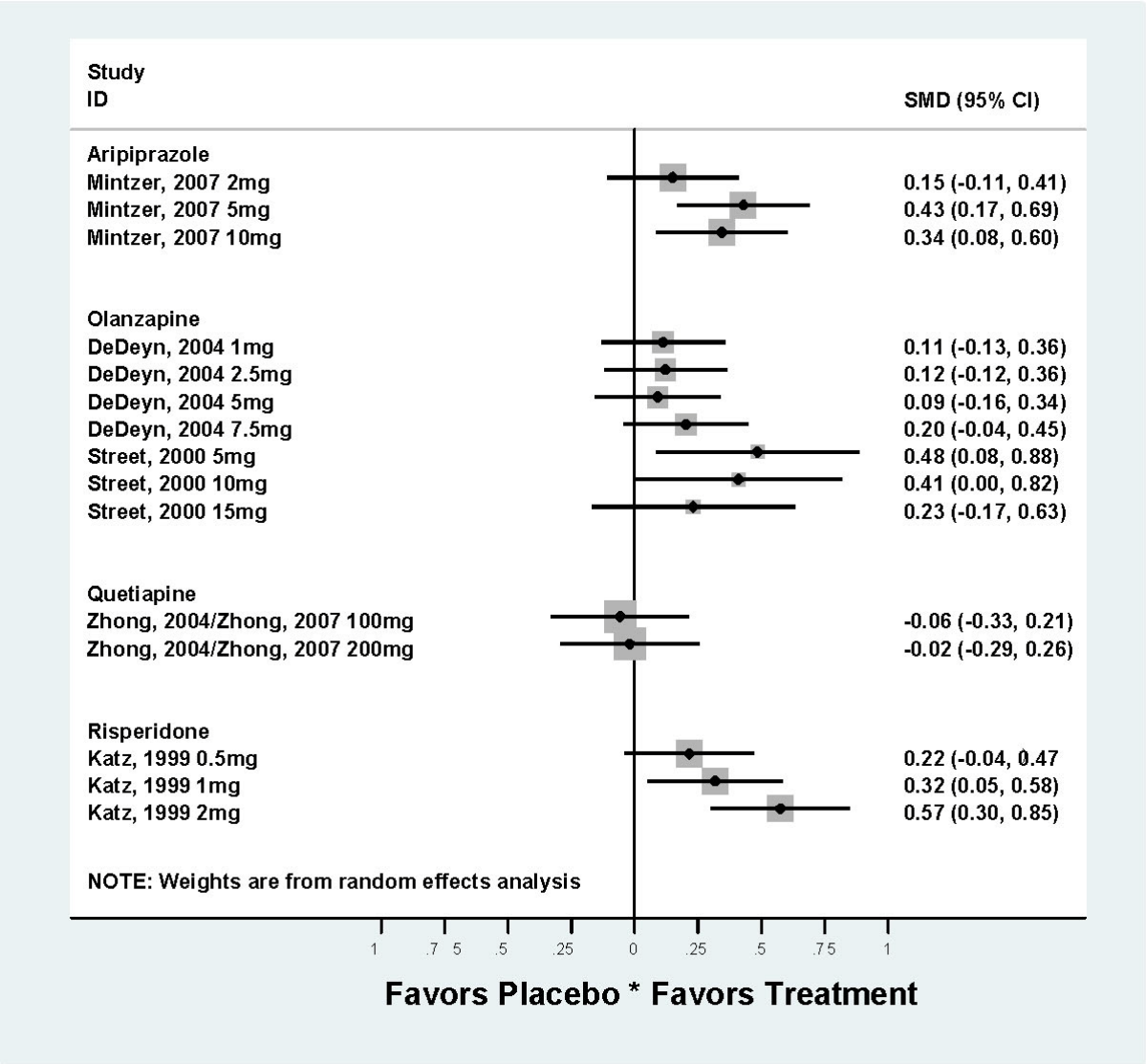


Figure 25. Dementia: PCTs with dose comparisons - Agitation



We found four depression PCTs in the non-elderly population that contained treatment arms for different doses used as augmentation.[146-149] All studied quetiapine and all contained both 150 mg and 300 mg arms. One also included a 50 mg arm.[149] Results of our meta-analyses are presented in Figures 26 and 27; outcomes were percentage of patients remitted or responded according to the MADRS. (Please see key question two section for further description of these outcomes.) Though three of the PCTs reported the 300 mg arm slightly superior to the 150 mg arm, the results were not statistically significant. The RR of entering remission, versus patients taking placebo, were 1.36 (95% CI 1.12, 1.64) for patients taking 150 mg and 1.51 (95% CI 1.25, 1.81) for patients taking 300 mg. Patients in the one 50 mg group had RR of 1.40 (95% CI 0.95, 2.07). The RR of responding, versus patients taking placebo, were 1.42 (95% CI 1.22, 1.67) for patients taking 150 mg and 1.43 (95% CI 1.25, 163) for patients taking 300 mg. Patients in the one 50 mg group had an RR of 1.41 (95% CI 1.07, 1.85).

Figure 26. Depression – MADRS % Remitted – Dose

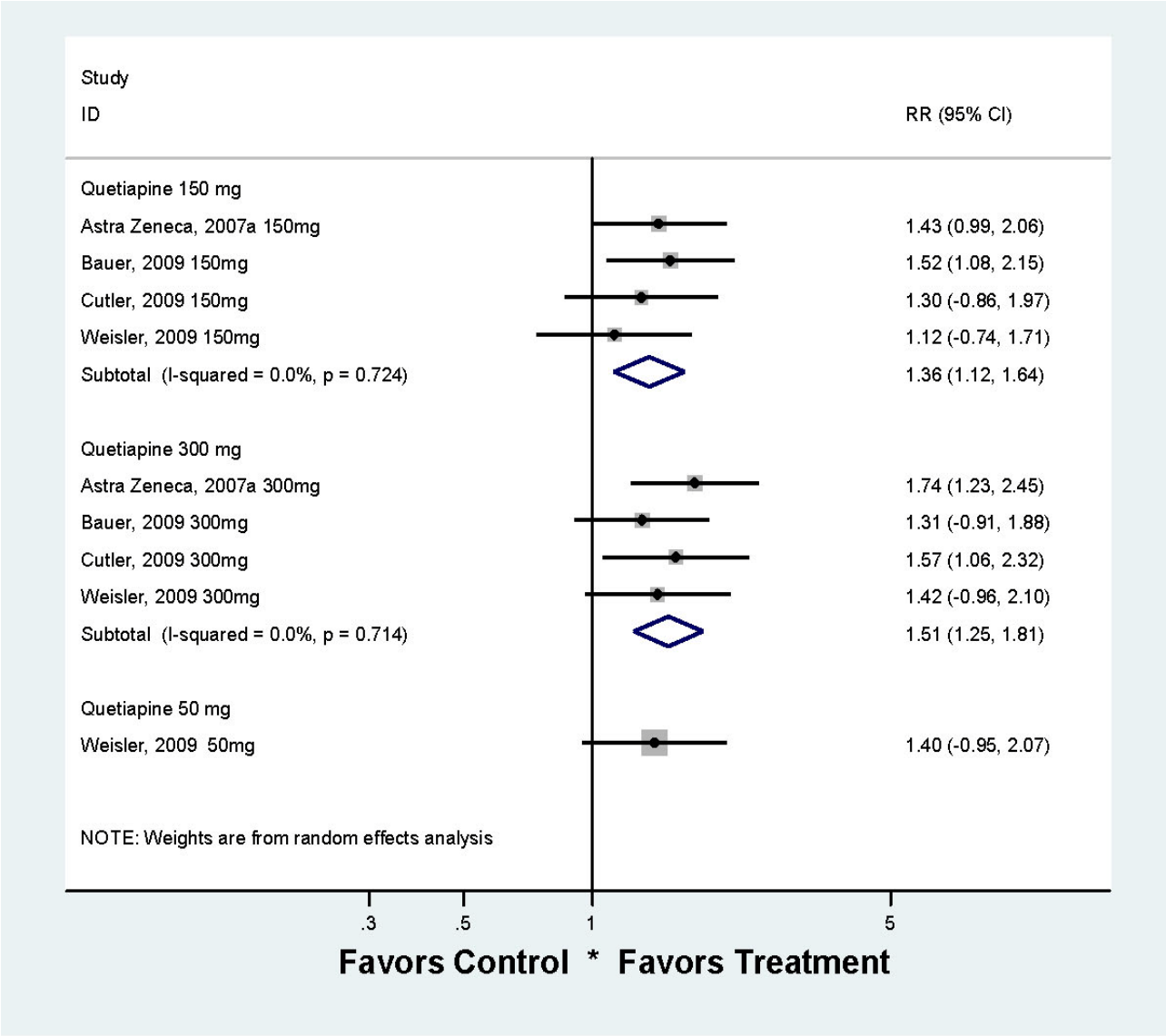
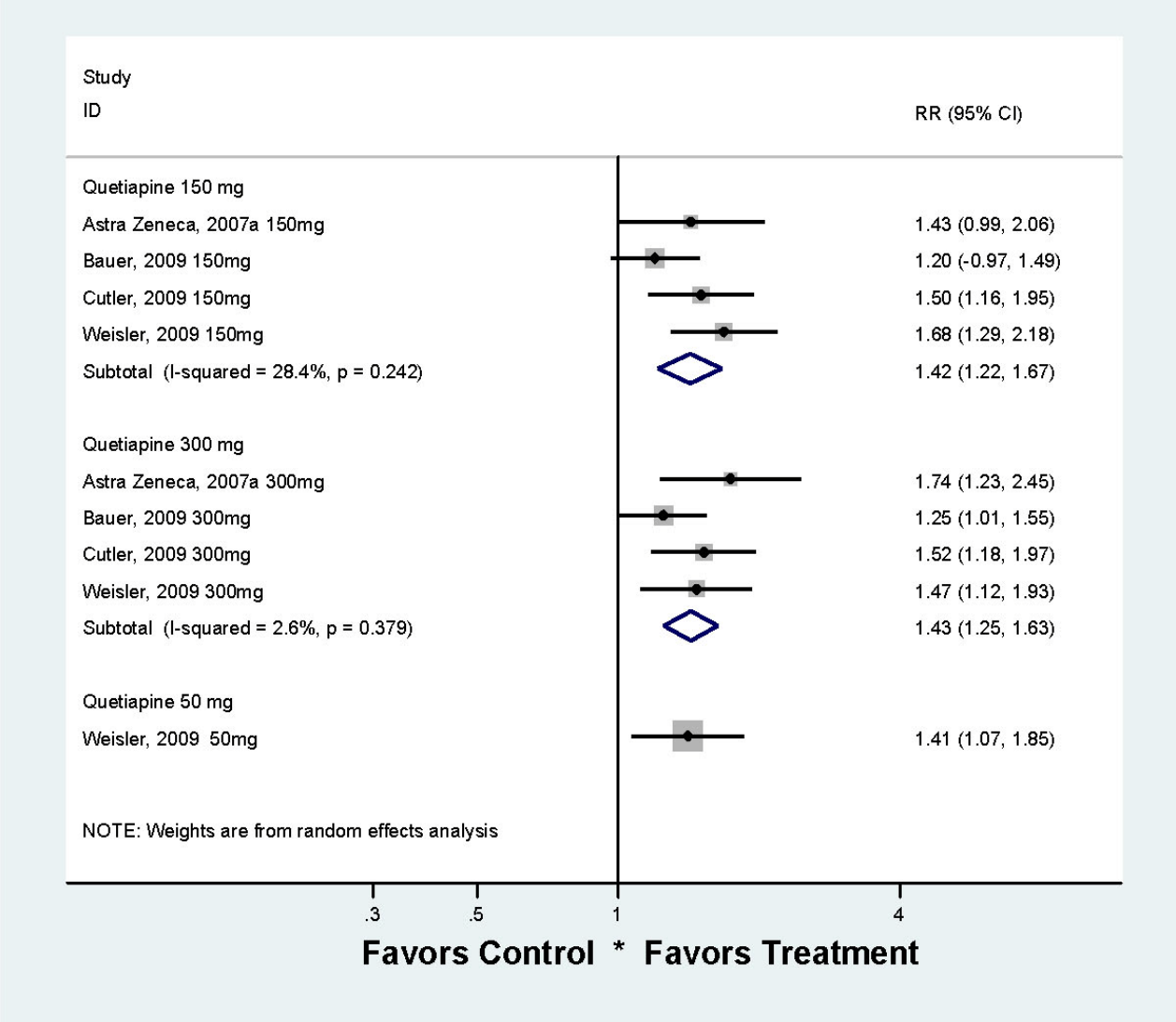


Figure 27. Depression – MADRS % Responded – Dose



Finally, one trial of borderline personality disorder treatment with olanzapine demonstrated improvement when 5-10 mg was used each day but no difference from placebo when 2.5mg was used.[204]

Timing. In regards to treatment duration, there were enough studies to pool data by duration for PTSD and eating disorders. Forest plots are presented in Figures 20 and 16, respectively, in the results section for Key Question Two. For the PTSD studies, there was no statistically significant improvement in CAPS scores for risperidone treatment over placebo at less than 12 weeks.[213, 216, 219] There were only two studies that reported improvement in CAPS scores for greater than 12 weeks, so those data could not be pooled. The one PTSD study that reported outcomes at both greater than and less than 12 weeks found risperidone not significantly different from placebo, regardless of time point.[219]

There were three eating disorder trials that measured changes in BMI with use of olanzapine at one and three months compared to placebo.[165, 167-168] There was no significant improvement, compared to placebo, at either of the time points.

There were two studies of the same population of borderline personality disorder patients receiving treatment with aripiprazole.[202-203] The first of these measured the population at eight weeks and the second at 18 months. Both time points demonstrated improvement in SCL-90 scores.

Discussion

In summary, for most conditions, there are too few studies comparing doses of atypical antipsychotic medications to draw a conclusion about a minimum effective dose. It appears that 150 mg quetiapine daily augmentation is equally efficacious as augmentation with 300 mg for MDD patients who respond inadequately to SSRIs, as measured by the percentage of remitters and responders according to the MADRS. More trials examining different doses of other atypicals for depression would help guide clinicians in treating this population. In addition, more dosage trials for treating conditions such as OCD, PTSD, and anxiety disorder would allow for pooling and comparison of results.

Though there is data regarding duration of treatment in PTSD, eating disorders, and borderline personality disorder, the outcome of treatment appears to be the same regardless of time point.

Chapter 4. Summary and Discussion

We conducted an extensive literature search, data abstraction, and meta-analyses, whenever possible, to assess the efficacy, comparative effectiveness, and safety of atypical antipsychotics for off-label indications. Since the submission of our original CER in 2006, many new high quality controlled trials have been published; we were able to add many to our prior quantitative analyses and conduct additional analyses on new conditions and adverse events. In this chapter, we describe the limitations of our review and meta-analyses and then present our conclusions. We also discuss the implications of our findings for future research.

Limitations

Our literature search procedures were extensive and included canvassing experts from academia and industry regarding studies we may have missed. However, the possibility of publication bias still exists. For the most part, our assessment did not yield any evidence of unexplained heterogeneity. Two exceptions include one outcome for depression and the YBOCS "percent of participants responded" outcome used in our OCD meta-analysis. In our analysis of atypicals as augmentation in treatment of major depressive disorder (MDD), possible publication bias appeared in studies reporting the percent of participants remitted according to the MADRS. We conducted additional efficacy meta-analyses using HAM-D outcomes; efficacy results were similar, but no heterogeneity was detected. Thus, our confidence that some atypicals are efficacious as augmentation of SSRIs or SNRIs for depression remains despite evidence of possible publication bias. Heterogeneity was also evident in studies assessing the efficacy of atypicals for OCD. This heterogeneity was likely due to patient enrollment criteria; studies used different definitions of "refractory" and "treatment resistant." Another published meta-analysis of atypicals for OCD[176] found similar efficacy results but no heterogeneity according to statistical tests.

Furthermore, when we reviewed the recent meta-analysis assessing death and the use of these drugs in persons with dementia, we learned of the existence of some manufacturer-supported trials, the published results of which we searched for and were not able to find, despite extensive computerized searches and requests to the manufacturers (we have since learned the results were not published). It is possible that other such unpublished trial results exist for the other conditions included in our report. We assume that publication bias may occur for all conditions, resulting in an overestimation of efficacy of these drugs and conditions.

An important limitation common to systematic reviews is the quality of the original studies included. In order to measure the quality of clinical trials we used the Jadad scale.[19] As empirical evidence regarding other study characteristics and their relationship to bias is lacking, we did not attempt to use other criteria. However, other aspects of the design and execution of a trial may be related to bias, but we do not yet have good measures of these elements. In our 2006 CER on off-label use of atypicals, we conducted a sensitivity analysis on the relationship between trial quality and effect size; the better quality trials reported an effect size 25 percent smaller than did lower quality trials. This finding increases the likelihood that a synthesis of results of all studies - whether narrative or quantitative – may produce inflated estimates of efficacy. As stated above,

the higher general quality of the dementia and depression augmentation studies led to a greater strength of evidence rating for those uses.

Applicability of research to the larger treatment population is important in interpreting the results of the included studies. The participation rate, the intended target population, representativeness of the setting, and representativeness of the individuals must be known to assess applicability. Such data were reported unevenly in the studies we reviewed. The dementia trials were most often conducted in nursing homes, hospitals, or assisted living facilities. According to our review on utilization patterns, these settings represent where atypicals are most often used in the elderly. Studies for other conditions were not particularly representative. For example, three of the four trials for ADHD were conducted in children with severe co-occurring conditions, such as bipolar disorder or mental retardation.

In the studies of atypicals as augmentation for SSRI or SNRI patients with major depressive disorder (MDD) it was often unclear whether patients were simultaneously undergoing psychotherapy. One trial[157] specifically stated that subjects were prohibited from initiating such therapy during the trial, but other reports were unclear on the issue. Thus, it is unclear whether treatment over and above the medication influenced the study results. As many depression patients are treated in primary care, it is important to note that subjects in the depression trials were recruited from both primary care and mental health centers.

We found only observational studies of atypicals for treatment of insomnia. Only one small study[172] included patients with insomnia as primary diagnosis. Others included patients with Parkinson's disease, MDD, polysubstance abuse withdrawal symptoms, and tamoxifen induced insomnia. Thus, the results of these studies should not be applied to the general population.

Conclusions

Tables 32 and 33 present the most clinically relevant findings. It is important to note that we found no trials, large observational studies, or utilization studies of the three newest atypicals (asenopine, iloperidone, and paliperidone) for off-label uses.

Table 32. Summary update: Efficacy of atypical antipsychotics for off-label use

Usage	Strength of evidence	2006 Findings	2010 Findings	2010 Conclusions
Dementia	High	A published meta-analysis of 15 placebo-controlled trials (PCTs) found small but statistically significant effects favoring treatment with risperidone and aripiprazole. There were effects that favored treatment with olanzapine for the BPRS and the NPI, but these differences were not statistically significant. Three studies of quetiapine were considered too clinically dissimilar to pool and results for the individual studies showed, with one exception, trends favoring treatment with quetiapine that did not reach conventional levels of statistical significance.	Overall – In our meta-analysis of PCTs, aripiprazole, olanzapine, quetiapine, and risperidone were superior to placebo as measured by total scores on BEHAVE-D, BPRS, and NPI. Psychosis – In our meta-analysis aripiprazole and risperidone were superiror to placebo, as measured by the psychosis subscales of the BEHAVE-AD, BPRS, and NPI. Results for olanzapine and quetiapine did not meet conventional levels of statistical significance. Agitation – In our meta-analysis, aripiprazole, olanzapine and risperidone were superior to placebo, as measured by the agitation subscales of the BEHAVE-AD, BPRS, NPI, and CMAI. Results for quetiapine did not meet conventional levels of statistical significance. Two head to head trials compared atypicals; none was found superior.	Aripiprazole, olanzapine, quetiapine and risperidone **have efficacy** as treatment for behavioral symptoms of dementia. There are no trials of ziprasidone for this use.

Depression – MDD: augmentation of SSRI / SNRI	Moderate – quetiapine, risperidone, aripiprazole Low – olanzapine, ziprasidone	Three trials assessed the combination of olanzapine and fluoxetine , one trial each assessed augmentation of various SRIs with risperidone, ziprasidone, and quetiapine, and one study assessed adding risperidone versus olanzapine to SSRI. The combination of olanzapine and fluoxetine was no better than fluoxetine alone in improvement of depressive symptoms at 8 weeks, but three trials reported more rapid improvement in depressive symptoms (at 2-4 weeks) with combination therapy using olanzapine or quetiapine. The one trial that directly compared augmentation therapy between olanzapine and risperidone reported no differences in outcome.	We conducted a meta-analysis using "response" to treatment as outcome. A responder was defined as someone who had at least a 50% reduction in depression score from randomization to follow up. Pooling trials that reported the HAM-D as outcome, the relative risk of responding for participants taking quetiapine or risperidone was significantly higher than for placebo. Olanzapine had only two trials, so pooling was not performed; the trials reported olanzapine superior to placebo. Other trials reported MADRS scores; the relative risk of responding for participants taking aripiprazole or quetiapine was significantly higher than those taking placebo. Risperidone and ziprasidone were included in one trial each; both trials reported the drug superior to placebo. One study compared olanzapine plus fluoxetine with olanzapine or fluoxetine alone. No placebo was used. Mean change in MADRS score was significantly higher with olanzapine plus fluoxetine. One trial compared ziprasidone at differing levels augmenting sertraline to sertraline alone. This trial found a greater improvement in CGI-S and MADRS scores augmenting with ziprasidone at 160mg than either augmentation with ziprasidone at 80mg or sertraline alone. However, there was no significant difference in HAMD-17, CGI-I or HAM-A scores.	Aripiprazole, quetiapine, and risperidone **have efficacy** as augmentation to SSRIs/SNRIs for major depressive disorder. Olanzapine and ziprasidone **may also have efficacy.**
Depression – MDD: Monotherapy	Moderate	The three olanzapine studies (above) also assessed its efficacy as monotherapy. Olanzapine alone was no better than placebo in improving symptoms at 6 or 12 weeks. Outcomes were too heterogeneous to allow pooling.	One new trial reported quetiapine increased time to next depressed event compared to placebo.	Same as 2006: Olanzapine **does not have efficacy** as monotherapy for major depressive disorder.

Obsessive compulsive disorder – augmentation of SSRI	Moderate – quetiapine, risperidone Low - olanzapine	12 trials used risperidone, olanzapine, and quetiapine as augmentation therapy in patients who were resistant to treatment with SSRI. Nine trials were sufficiently similar clinically to pool. Atypical antipsychotics had a clinically important benefit (measured by the Yale-Brown Obsessive-Compulsive Scale) when used as augmentation therapy. Relative risk of "responding" significant for augmentation with quetiapine and risperidone. There were too few studies of olanzapine augmentation to permit separate pooling of this drug.	Two new trials of quetiapine were added to those included in our 2006 meta-analysis. The new results echoed those of our original CER, finding quetiapine and risperidone superior to placebo, as measured by changed in the Yale Brown Obsessive Compulsive Scale (YBOCS). There were too few studies (two) to permit separate pooling for olanzapine; both trials reported olanzapine superior to placebo. One new head to head trial found no difference in effect between olanzapine and risperidone as SSRI augmentation. One new head to head trial found quetiapine more efficacious than ziprasidone as SSRI augmentation. One new trial compared quetiapine to clomipramine as SSRI augmentation. Quetiapine produced a significant reduction in YBOCS score, while clomipramine did not.	Quetiapine and risperidone **have efficacy** in improving OCD symptoms when used as an adjunct to SSRI in treatment refractory patients. Olanzapine may also **have efficacy.** Quetiapine is more **efficacious** than ziprasidone and clomipramine for this purpose.
Obsessive compulsive disorder – augmentation of citalopram	Low- quetiapine Very low - risperidone	One trial of risperidone reported no differences between groups in achieving a response to therapy, but patients maintained on risperidone had a significantly longer period of time to relapse compared to placebo (102 days v. 85 days)	Two new trials found quetiapine superior to placebo as augmentation for citalopram, according to YBOCS and CGI-I scores.	Quetiapine **is efficacious** as augmentation to citalopram in OCD patients. Risperidone may also be **efficacious.**
Post traumatic stress disorder	Moderate - risperidone	Four trials of risperidone and two trials of olanzapine, each of at least 6 weeks duration, treated patients with PTSD. Three trials enrolled men with combat-related PTSD; these showed a benefit in sleep quality, depression, anxiety, and overall symptoms when risperidone or olanzapine was used to augment therapy with antidepressants or other psychotropic medication. Three trials of olanzapine or risperidone as monotherapy for abused women with PTSD were inconclusive regarding efficacy.	Three new trials of risperidone were found, allowing us to conduct a meta-analysis using the Clinician Administered PTSD Scale (CAPS) as outcome. Risperidone was superior to placebo. There were too few olanzapine studies (two) to pool; one reported olanzapine superior to placebo, while one did not. We also conducted a meta-analysis by condition; atypicals were efficacious for combat-related PTSD but not PTSD in abused women.	Risperidone is **efficacious** in reducing combat-related PTSD symptoms when used as an adjunct to primary medication.

Personality disorders - borderline	Moderate – aripiprazole Low – olanzapine, quetiapine, ziprasidone	Three trials provide evidence that olanzapine is superior to placebo & may be superior to fluoxetine. The benefit of adding olanzapine to dialectical therapy in one trial was small. Aripiprazole was superior to placebo in one small trial.	One new trial found aripiprazole superior to placebo in improving SCL-90, HAM-D, and HAM-A scores at 8 months and less self-injury at 18 months. One new trial of ziprasidone found no significant difference in CGI-BPD, depressive, anxiety, psychotic or impulsive symptoms compared to placebo at 12 weeks. Two new trials of olanzapine found no difference from placebo in any outcomes, while another new trial of olanzapine found greater change in ZAN-BPD scores at 12 weeks, compared with placebo. One new trial found quetiapine superior to placebo on BPRS, PANSS scales. Due to heterogeneity of outcomes, we could not perform a meta-analysis.	Trials using atypical antipsychotics for treatment of borderline personality disorder (BPD) have shown mixed results. Due to heterogeneity of outcomes, we could not perform a meta-analysis. Olanzapine had **mixed results** in 7 trials, aripiprazole was found **efficacious** in two trials, quetiapine was found **efficacious** in one trial, and ziprasidone was found **not efficacious** in one trial.
Personality disorders - schizotypal	Low	Risperidone was superior to placebo in one small trial.	One new small trial of risperidone found no difference from placebo on a cognitive assessment battery.	Risperidone had **mixed results** when used to treat schizotypal personality disorder in two small trials.
Tourette's syndrome	Low	Risperidone was superior to placebo in one small trial, and it was at least as efficacious as pimozide or clonidine for 8 to 12 weeks of therapy in the three other trials. One trial of ziprasidone showed variable efficacy compared to placebo.	No additional trials.	Same as 2006: Risperidone **is at least as efficacious as pimozide or clonidine** for Tourette's syndrome.
Eating disorders	Moderate	Not covered.	Four trials of olanzapine were found; three reporting Body Mass Index (BMI) could be pooled. There was no difference in change in BMI at either one or three months compared to placebo.	Olanzapine **has no efficacy** in increasing body mass in eating disorder patients.
Anxiety	Moderate	Not covered.	Three placebo-controlled trials of quetiapine for Generalized Anxiety Disorder (GAD) could be pooled; relative risk of responding on HAM-A favored the quetiapine group. One head to head trial showed no difference between risperidone and paroxetine on HAM-A score improvement.	Quetiapine **has efficacy** as treatment for Generalized Anxiety Disorder

Attention deficit / hyperactivity disorder – no co-occurring disorders	Low	Not covered.	One trial showed risperidone superior to placebo in reducing scores on the Children's Aggression Scale – Parent version (CAS-P).	Risperidone may be **efficacious** in treating children with ADHD with no serious co-occurring disorders.
Attention deficit / hyperactivity disorder - mentally retarded children	Low	Not covered.	One trial showed risperidone led to greater reduction in SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than methylphenidate.	Risperidone **may be superior to methylphenidate** in treating ADHD symptoms in mentally retarded children.
Attention deficit / hyperactivity disorder - bipolar children	Low	Not covered.	Two trials of aripiprazole showed no effect on SNAP-IV (Swanson, Nolan, and Pelham teacher & parent rating scale) scores than placebo.	Aripiprazole is **inefficacious** in reducing ADHD symptoms in children with bipolar disorder.
Substance abuse - alcohol	Moderate – aripiprazole Low – quetiapine	Not covered.	Two trials of aripiprazole and one of quetiapine reported % of patients completely abstinent during follow-up. In our pooled analysis, the effect versus placebo was insignificant.	Aripiprazole is **inefficacious** in treating alcohol abuse / dependence. Quetiapine may also be **inefficacious.**
Substance abuse - cocaine	Low	Not covered.	Two trials of olanzapine and one of risperidone reported there was no difference in efficacy versus placebo as measured by the Addiction Severity Index (ASI).	Olanzapine is **inefficacious** in treating cocaine abuse / dependence. Risperidone may also be **inefficacious.**
Substance abuse – meth-amphetamine	Low	Not covered.	One trial found aripiprazole inefficacious in reducing use of intravenous amphetamine, as measured by urinalysis. Another trial found aripiprazole inefficacious in reducing craving for methamphetamine.	Aripiprazole is **inefficacious** in treating methamphetamine abuse / dependence.
Substance abuse – methadone clients	Low	Not covered.	One trial of methadone clients found no difference between risperidone and placebo in reduction of cocaine or heroin use.	Risperidone is an **inefficacious** adjunct to methadone maintenance.
Insomnia	Very low.	Not covered.	No trials found. Two observational studies of olanzapine and four of quetiapine found promising improvements in sleep quality and sleep onset.	Olanzapine and quetiapine **may be efficacious** in improving insomnia symptoms.

Table 33. Summary update: Safety of atypical antipsychotics for off-label use

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Weight gain – Elderly patients	Greater weight gain for olanzapine patients than those taking quetiapine or risperidone, according to one large trial (CATIE-AD). Patients taking any of these three drugs gained more weight than placebo patients.	More common in patients taking olanzapine than risperidone or conventional antipsychotics, particularly if their BMI was less than 25 at baseline, according to a large cohort study.	More common in patients taking olanzapine and risperidone, according to our meta-analysis.
Weight gain – Adults 18 - 64	More common in olanzapine patients than ziprasidone patients in one trial.	More common among patients taking olanzapine than patients taking conventional antipsychotics in three trials. More common in patients taking aripiprazole than patients taking conventional antipsychotics in one trial. More common among patients taking olanzapine than patients taking mood stabilizers in two trials.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone, according to our meta-analysis.
Weight gain – Children & adolescents	No evidence reported.	No difference between clonidine and risperidone in one trial.	More common in patients taking risperidone in our meta-analysis. No difference in one small PCT of ziprasidone.
Mortality - Elderly patients	No difference between olanzapine and risperidone according to a meta-analysis of six trials of olanzapine published in 2006.	Five large cohort studies compared mortality in elderly patients taking atypical and conventional antipsychotics. Three of these studies found a significantly higher rate of death with conventional antipsychotics, while two found no statistical difference in mortality between the drug classes	The difference in risk for death was small but statistically significant for atypicals, according to a 2006 meta-analysis which remains the best available estimate. Sensitivity analyses found no difference between drugs in the class. Patients taking atypicals had higher odds of mortality than those taking no antipsychotics in the two cohort studies that made that comparison. There are no trials or large observational studies of ziprasidone in this population; therefore, we can not make conclusions regarding safety here.
Endocrine / diabetes – Elderly patients	No evidence reported.	No evidence reported.	No difference in endocrine events in risperidone patients in one PCT. Regarding diabetes, risk was elevated but not statistically significant in one industry-sponsored study of olanzapine patients.

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Endocrine / diabetes – Adults 18 - 64	Diabetes more common in patients taking olanzapine than patients taking risperidone in one trial.	No evidence reported.	Endocrine events more common in patients taking quetiapine, risperidone, and ziprasidone in one PCT each. More common in quetiapine in five pooled PCTs. More common in olanzapine in two pooled PCTs. Diabetes more common in patients taking quetiapine in five pooled PCTs; however, the pooled odds ratio was elevated at 1.40 but not statistically significant. More common in olanzapine patients in one PCT; the odds ratio of 5.14 was not statistically significant, with very wide confidence intervals (0.6 to 244). Lower odds of diabetes in risperidone patients in one large observational study
CVA - Elderly patients	No evidence reported.	No difference of risk by whether the patients used a conventional, atypical, or no antipsychotics therapy, according to a large study of Veterans Administration and Medicare patients. The only risk was in patients with the vascular dementia subtype who received risperidone; they had a decreased risk of CVA compared to haloperidol, whereas olanzapine and quetiapine did not.	More common in risperidone patients according to four PCTs pooled by the manufacturer. In our new meta-analysis of PCTs, risperidone was the only drug associated with an increase. More common in olanzapine according to five PCTs pooled by the manufacturer.
EPS - Elderly patients	More common in patients taking aripiprazole and risperidone patients than patients taking quetiapine in one large trial (CATIE-AD).	No evidence reported.	More common in patients taking aripiprazole and risperidone, according to our meta-analysis. Quetiapine was not associated with an increase. More common in olanzapine in one PCT.
EPS – Adults 18 - 64		Less likely in patients taking quetiapine than mood stabilizers in one small trial. Less likely in patients taking olanzapine or aripiprazole than patients taking conventional antipsychotics in one trial each.	More common in patients taking aripiprazole, quetiapine, and ziprasidone according to our meta-analysis.

Adverse event	Head to head comparisons	Active comparisons	Placebo comparisons
Sedation – Adults, elderly patients	More common in elderly patients taking olanzapine or quetiapine than risperidone according to our analysis, but not quite statistically significant. In adults 18 – 64, more common in patients taking quetiapine than patients taking risperidone in two trials.	No evidence reported.	More common in patients taking aripiprazole, olanzapine, quetiapine, and risperidone, according to our meta-analysis.
Sedation – Children and adolescents		No difference in one small trial of clonidine versus risperidone. More patients on haloperidol than risperidone reported sleep problems in one trial.	Less common in aripiprazole patients than placebo patients in one PCT. No difference from placebo in one small PCT of ziprasidone.

Future Research

The overarching finding of this review is that although atypical antipsychotic medications are being used for a large number of off-label uses, we were able to find moderate to strong evidence of efficacy for only a few of the drugs and only a few of the off-label uses. Most of the evidence is concentrated in the drugs risperidone, olanzapine, and quetiapine, and the off-label indications of dementia, depression, and obsessive-compulsive disorder. For the newly approved atypicals (asenapine, iloperidone, and paliperidone), we found no clinical trials assessing their use for any off-label condition, and for some off-label uses, we found no or only a small number of trials. Head-to-head comparisons of atypical antipsychotic drugs for off-label uses are few, and evidence from placebo-controlled trials for off-label uses suggests that efficacy differs between drugs, meaning that the assumption of a "class effect" for atypical antipsychotics may be unwarranted. This means that each drug is going to require its own evaluation of efficacy for each off-label indication, which is a large task; and then drugs demonstrated to be efficacious will need to be tested head-to-head in trials of comparative effectiveness.

With respect to use in individual off-label conditions, we offer the following thoughts.

ADHD. Regarding ADHD, we found three placebo-controlled and one active-control trials. Two of these studied risperidone and two studied aripiprazole. Though these did find some effectiveness for ADHD, the trials utilized differing measures of efficacy and the patient populations differed in severity of illness and comorbid conditions. For these reasons, the trials cannot be pooled and overall effectiveness in ADHD still needs to be established for each medication. Future research should look at utilizing one standard measure of ADHD or including multiple measures in order for them to be compared. In addition, it is unclear if other atypical antipsychotic medications, such as quetiapine, olanzapine and aripiprazole are also being used for ADHD. As we found no trials of their efficacy, future research should include studies of these medications.

Anxiety. Though there were 15 placebo controlled trials of atypical agents in anxiety, only three of them were clinically similar enough to pool. These trials used quetiapine. There were mixed reports of efficacy for the other atypicals and there were no studies of anxiety treatment with aripiprazole. Future research needs to include additional studies of the various atypical agents. As the HAM-A was the most commonly used measure, if these future trials utilized the HAM-A, it will be possible to compare across trials.

Dementia. Given the concern over serious adverse events such as mortality, knowledge of the efficacy of atypical antipsychotics in the demented elderly is of paramount importance. We did find evidence that aripiprazole, olanzapine, risperidone, and quetiapine were superior to placebo. There were no trials of ziprasidone in dementia. An assessment of the net effect of effectiveness compared to the side effect burden would be useful in future studies.

Depression. There were only enough trials of quetiapine and risperidone to pool to show efficacy when used an augmentation agent. Olanzapine augmentation was shown to be superior to placebo but there were only two trials. Therefore, further research of olanzapine in treating

depression is suggested. Likewise, there was only one placebo controlled trial of ziprasidone in depression. Though it was found to be superior, further studies to confirm this finding are required.

Eating Disorders. As weight gain is a common side effect experienced during treatment of other conditions with olanzapine, the assumption has been that this side effect could be exploited for therapeutic benefit as a treatment of eating disorders. Though commonly used clinically, the four trials of olanzapine in eating disorders found that it led to no statistically significant difference in BMI. Mechanistic studies to explain differences in those with eating disorders from those with other psychiatric conditions may elucidate why weight gain occurs in some populations but not others.

Insomnia. Insomnia is another condition where the side effects seen during the use of atypical antipsychotics are exploited for treatment. Atypicals, particularly olanzapine and quetiapine, are commonly sedating. Therefore, they are clinically used to treat insomnia. Clinical trials are needed to rigorously test the conclusions from observational studies that olanzapine and quetiapine are useful in promoting sleep quality and sleep onset. Placebo controlled trials confirming their efficacy are necessary before reaching any conclusions.

OCD. There were several trials reporting the efficacy of quetiapine as an augmentation agent in OCD and a few of risperidone. Further studies of olanzapine and aripiprazole are required, in order to assess their efficacy. In addition, further trials comparing the atypical antipsychotic agents to the current standards of treatment would be helpful in order to know at which point of treatment failure there benefit is greatest. For example, one trial found that quetiapine had greater efficacy in reducing the YBOCS score than clomipramine, though clomipramine is currently a more widely recommended treatment for resistant OCD. If further trials confirmed this result, atypical antipsychotics could be placed higher on an algorithm for recommended treatment.

Personality Disorders. Personality disorders have remained a difficult area for clinicians, leading to continued exploration for successful treatments. Unfortunately, our ability to reach strong conclusions is hindered by the heterogeneity of the trials reviewed. Future research will need to have standard outcomes so that results across trials can be compared. In our review, olanzapine and risperidone had mixed results, quetiapine and aripiprazole were found to have some efficacy while ziprasidone did not. However, there were too few trials to allow for clinicians to predict the effect of a particular agent for a particular patient. Before reaching conclusions regarding clinical use further research, with comparable outcomes, is necessary.

PTSD. There were studies finding efficacy for risperidone and olanzapine for the symptoms of PTSD. An issue in PTSD is the question of whether the results are affected by gender. Our review found that the atypicals showed efficacy in male combat veterans but not female victims of civilian trauma. Whether this signifies that efficacy differs by gender or rather that combat trauma is more amenable to treatment with atypicals than civilian trauma requires further research to elucidate.

Substance Abuse. Trials of atypical antipsychotic treatment of substance abuse did not find them superior to placebo. Future research is needed to establish a role, if any, in the use of atypical antipsychotic drugs in the treatment of substance abuse.

Tourette's Syndrome. Other than the efficacy demonstrated with risperidone, there is only one placebo controlled trial of another atypical antipsychotic, ziprasidone, as a treatment for Tourette's syndrome. Additional trials are needed before any conclusions can be reached regarding the other atypicals.

In addition to the further research recommended for the various conditions, there is almost no existing evidence about how treatment efficacy may vary within populations, including variations due to gender, race, ethnicity, or other comorbidities. In addition, existing evidence about the effect of baseline severity of disease is too heterogeneous to allow us to draw conclusions. In future research, standardized measures of disease severity might allow for greater knowledge of the patient populations who would benefit from treatment with atypical agents.

Regarding adverse effects of the atypical antipsychotics, existing evidence varies by drug and by description of the adverse event. It would facilitate assessments if future studies contained a standardized list of assessed side effects. As many trials report only those effects observed, we are unable to compare between trials for many of the side effects.

Another area where clinical guidance is needed is in the dosages required to achieve effects in off-label indications. The dosages used in off-label indications varied from those used in on-label indications. However, there were few trials that looked at a comparison of dosage effectiveness. As populations of patients and the measures used to evaluate them often differed between trials, a dosage comparison across trials was generally not possible. More research, examining differing dosages within the same population, is required in order to guide clinicians in the appropriate doses to prescribe. A similar issue is that of treatment length. More research examining responses at various time points would be helpful in determining how long treatment is required. Given the risk of side effects when using these agents, clinicians need to know when a result is expected to prevent continuing an ineffective agent, unnecessarily.

Newer agents, such as asenapine, iloperidone and paliperidone cannot be assumed to have efficacy and harms similar to the older atypical antipsychotics, since the evidence to date does not support that there is a general "class effect" in terms of either efficacy or harm for most off-label indications. Trials assessing the newer agents' efficacy and safety are necessary in each of the treatment areas if they are to be prescribed for off-label use.

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Abbreviations and Acronyms Glossary

ACES	Agitation-Calmness Evaluation Scale
ACTeRS	ADD-H Comprehensive Teachers Rating Scale
ADAS	Alzheimer's Disease Assessment Scale
ADDES-S	Attention-Deficit Disorders Evaluation Scale: Secondary-Age Student
ADHD	Attention-Deficit Hyperactivity Disorder
ADHD-SC4	ADHD Symptom Checklist
AHRQ	Agency for Healthcare Research and Quality
ASEBA	Achenbach System for Empirically Based Assessment
ASI-drug	Addiction Severity Index Drug Composite Score
BAI	Beck Anxiety Inventory
BASC-2	Behavior Assessment System for Children-2
BDI	Beck Depression Inventory
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BMI	Body Mass Index
BPD	Borderline Personality Disorder
BPRS	Brief Psychiatric Rating Scale
BRMES	Bech-Rafaelson Melancholia Scale
BSI	Brief Symptom Inventory
CAARS	Conners' Adult ADHD Rating Scales
CAPS	Clinician-Administered PTSD Scale
CAS-P	Children's Aggression Scale - Parent Version
CAS-T	Children's Aggression Scale - Teacher Version
CBT	Cognitive Behavioral Therapy
CCQ	Cocaine Craving Questionnaire
CENTRAL	Cochrane Central Register of Controlled Trials
CER	Comparative Effectiveness Review
CES-D	Center for Epidemiologic Studies Depression Scale
CGI-I	Clinical Global Impression Scale - Improvement subscale
CGI-S	Clinical Global Impression Scale - Severity Subscale
CI	Confidence Interval
CIBIC	Clinician’s Interview-Based Impression of Change
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CMAI	Cohen-Mansfield Agitation Inventory
CSCAADD	Copeland Symptom Checklist for Adult Attention-Deficit Disorders
CVA	Cerebrovascular Accident
DARE	Database of Abstracts of Reviews of Effects
DAS-A	Daily Assessment of Symptoms - Anxiety
DIS-Q	Dissociation Questionnaires
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th. Edition
E-BEHAVE-AD	Empirical Behavioral Pathology in Alzheimer's Disease Rating Scale
ED	Emergency Department
EDEQ	Eating Disorders Examination Questionnaire Version
EMBASE	Biomedical and Pharmacological Bibliographic Database

EPC	Evidence-based Practice Center
EPS	Extrapyramidal Symptoms
FDA	Food and Drug Administration
FGA	First Generation Antipsychotics
GAD	Generalized Anxiety Disorder
GAF	Global Assessment of Functioning Scale
HAM-A	Hamilton Anxiety Rating Scale
HAM-D/HDRS	Hamilton Depression Rating Scale
ISI	Insomnia Severity Index
ISQ	Insomnia Symptom Questionnaire
KQ	Key Question
MADRS	Montgomery-Asberg Depression Rating Scale
MDD	Major Depressive Disorder
MMSE	Mini Mental Status Exam
MR	Mentally Retarded
NC	Not Calculated
NNH	Number Needed to Harm
NPI	Neuropsychiatric Inventory
NPI-NH	Neuropsychiatric Inventory, Nursing Home
OAS-M	Overt Aggression Scale-Modified
OCD	Obsessive-Compulsive Disorder
PANSS	Positive and Negative Symptom Scale
PCT	Placebo Controlled Trial
PD	Personality Disorders
PDC	Depression Cluster
PRS	Parent's Rating Scale
PSQI	Pittsburgh Sleep Quality Inventory
PTSD	Posttraumatic Stress Disorder
QEWP-R	Questionnaire on Eating and Weight Patterns- Revised
RCT	Randomized Controlled Trial
RR	Relative Risks
SCHIP	State Children’s Health Insurance Program
SCL-90	Symptom Checklist-90
SCL-90-R	Symptom Checklist-90-revised
SDS	Sheehan Disability Scale
SF36	Medical Outcomes Study 36-Item Short-Form Health Survey
SIAB	Structured Interview for Anorexia and Bulimia
SNAP-IV	Swanson, Nolan and Pelham Rating Scale
SPI	Medical Outcomes Study (MOS) Sleep Problem Index
SRC	Scientific Resource Center
SRI	Serotonin Reuptake Inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
STAXI	State-Trait Anger Expression Inventory
TEP	Technical Expert Panel
TMR	Therapist Monitoring Record
TSSR	Tic Symptom Self Report

VA	Veterans Administration
WURS	Wender Utah Rating Scale
Y-BOCS	Yale-Brown Obsessive-Compulsive Scale
YGTSS	Yale Global Tic Severity Scale
ZAN-BPD	Zanarini Rating Scale for Borderline Personality Disorder