Draft Comparative Effectiveness Review

Number XX

Preventive Pharmacological Treatments for Migraine

Part A: Adults
Part B: Children

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

This draft comparative effectiveness review is distributed solely for the purpose of pre-release peer review. It has not been otherwise disseminated by AHRQ. The draft report should not be cited or referenced. In draft form, it does not represent, and should not be construed to represent, an AHRQ determination or policy. After peer review, the final report may be used, in whole or in part, to inform the development of clinical practice guidelines, other quality enhancement tools, methodologic guidance for systematic review, or to inform reimbursement and coverage policies. AHRQ or U.S. Department of Health and Human Services endorsement of such derivative products may not be stated or implied.

Contract No.

Prepared by:

Investigators:

AHRQ Publication No. xx-EHCxxx

<Month Year>

Statement of Funding and Purpose

This report is based on research conducted by an Evidence-based Practice Center (EPC) under contract to the Agency for Healthcare Research and Quality (AHRQ), Rockville, MD (Contract No. xxx-xx-xxxxx-x). The findings and conclusions in this document are those of the authors, who are responsible for its contents; the findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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

Public Domain Notice
This document is in the public domain and may be used and reprinted without special permission. Citation of the source is appreciated.

Disclaimer Regarding 508-Compliance
Persons using assistive technology may not be able to fully access information in this report. For assistance contact info@ahrq.gov.

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

Preface

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

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

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

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

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

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

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

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

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

Suchitra Iyer, Ph.D.
Task Order Officer
Center for Outcomes and Evidence
Agency for Healthcare Research and Quality

Part A. Preventive Pharmacological Treatments for Migraine in Adults

Structured Abstract

Objectives: To assess comparative effectiveness and safety of preventive pharmacological treatments for community-dwelling adults with episodic or chronic migraine.

Data Sources: We searched major electronic bibliographic databases and trial registries up to March 29, 2012.

Review Methods: We performed a systematic review of published in English randomized controlled clinical trials (RCTs) that examined prevention of episodic or chronic migraine and rates of complete cessation of migraine, reduction of monthly migraine frequency by ≥50 percent, reduction in migraine-related disability, and improvement in quality of life with Food and Drug Administration approved and off-label drugs. Studies that compared drugs with nonpharmacological interventions and drug management interventions were also eligible. We calculated absolute risk differences, pooled them with random-effects models and with Bayesian network meta-analysis, and calculated numbers of outcome events attributable to treatments per 1,000 treated.

Results: Episodic or chronic migraine prevention in adults was examined in 308 references, including 183 RCTs that enrolled 48,875 adults with an average of six migraine attacks/month. Middle-aged Caucasian women constituted a majority of enrollees. Few trials reported the proportion of obese subjects, but many subjects were overweight; the average body mass index was 25.8 kg/m^2. More than half of the RCTs defined migraine according to the International Headache Society definition. Studies excluded adults with severe medical or psychiatric illnesses or contraindications to examined drugs. Strength of evidence was mostly low due to risk of bias and imprecision in individual RCTs and pooled estimates. RCTs examined 60 drugs from 16 drug classes. Botulinum toxin was more effective than placebo in reducing monthly chronic migraine attacks by ≥50 percent (three RCTs of 459 adults, low strength of evidence) with inconsistent improvement in quality of life. Reduction in episodic monthly migraine frequency by ≥50 percent was examined in 84 RCTs with 41 drugs from 13 drug classes. All approved drugs (botulinum toxin, topiramate, divalproex, timolol, and propranolol), off-label beta blockers, ACE inhibitors, and the angiotensin II receptor antagonist candesartan were better than placebo in reducing episodic monthly migraine frequency by ≥50 percent. Drugs resulted in clinical improvement in 200 to 400 patients per 1,000 treated. Intolerable adverse effects leading to treatment discontinuation were examined in 52 RCTs with 28 drugs from eight drug classes. Topiramate, divalproex, off-label antiepileptics, antidepressants, and ergot alkaloids resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Limited direct evidence of comparative effectiveness from head-to-head RCTs demonstrated no consistent significant differences in outcomes. Indirect adjusted frequentist analysis of the comparative effectiveness of 17 effective (better than placebo) drugs demonstrated that the

angiotensin II receptor blocker candesartan was more effective than topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline. Network Bayesian meta-analysis demonstrated that angiotensin inhibiting drugs (captopril, lisinopril, candesartan), were the most effective and safest for episodic migraine prevention in adults who have no contraindications to examined drugs.

Individual RCTs of drug-management interventions offered low strength of evidence that compared to usual care, multidisciplinary team care improved quality of life and reduced migraine-related disability; a headache management program resulted in complete cessation of migraine; a minimal-contact cognitive-behavioral program improved patient satisfaction with treatments; headache school decreased overuse of drugs for acute headache attacks and reduced migraine disability; pharmaceutical care improved self-efficacy; and an intensive pharmaceutical care campaign had no statistically significant impact on use of acute drug utilization.

Conclusions: For episodic migraine, off-label angiotensin inhibiting drugs have the best benefits-to-harms profile. Approved and off-label beta blockers are effective without bothersome harms. Approved antiepileptic drugs are effective but result in intolerable adverse effects. Long-term preventive benefits and adherence with drugs are unknown. Evidence on improving quality of life was inconsistent across individual drugs. Evidence for individualized treatment decisions is very limited. Future research should examine the role of patient characteristics on drug benefits and safety.

Contents

Executive Summary ES-1
Introduction 1
Key Questions 2
Methods 4
Search Strategy 4
Eligibility 4
Inclusion Criteria 4
Exclusion Criteria 5
Risk of Bias Assessment 5
Grading the Evidence for Each Key Question 6
Assessing Applicability 6
Data Extraction 6
Data Synthesis 7
Results 10
Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults? 10
a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment? 11
Prevention of Chronic Migraine 11
Muscle Relaxants 11
Prevention of Episodic Migraine 12
Antiepileptics 12
Beta Blockers 13
Off-label Drugs 14
Off-label Antiepileptic Drugs 14
Beta Blockers 14
Antidepressants 15
Calcium Channel Antagonists 15
Angiotenin Converting Enzyme Inhibitors 16
Angiotensin II Receptor Antagonists 16
Antiadrenergics 17
Ergot Alkaloids 17
Leukotriene Receptor Antagonists 17
Nonsteroid Anti-inflammatory Drugs 17
Antipsychotic Drugs 17
Antidementia Drugs 18
b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments? 18
Approved Drugs 18
Muscle Relaxants 18
Antiepileptics 19
Beta Blockers 19
Off-label Drugs 21

Off-label Beta Blockers 21
Antidepressants 21
Indirect Evidence of Comparative Effectiveness of Preventive Drugs 22
c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments? 23
Beta Blockers 23
Antidepressants 23
d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone? 23
Beta Blockers 23
Antidepressants 24
e1.How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? 24
Muscle Relaxants 24
Antiepileptics 24
Beta Blockers 25
Off-label Beta Blockers 25
Antidepressants 25
e2.How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results? 25
Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults? 55
a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment? 55
Muscle Relaxants 55
Antiepileptics 55
Beta Blockers 56
Off-label Drugs 57
Antiepileptics 57
Beta Blockers 58
Antidepressants 58
Ergot Alkaloids 58
Angiotensin Converting Enzyme Inhibitors 59
Angiotensin II Antagonists 59
Calcium Channel Antagonists 59
NSAID 59
b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments? 59
Muscle Relaxants 59
Beta Blockers 60
Off-label Drugs 61
Off-label Beta Blockers 61
Antidepressants 61
Ergot Alkaloids 62

Indirect Evidence of Comparative Safety of Drugs for Migraine Prevention in Adults.....62
c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results? 62
Question 3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults? 80
Muscle Relaxants 80
Antiepileptics 80
Antidepressants 81
Selective Calcium Channel Blockers 81
Discussion 82
Key Messages 84
Efficacy and Comparative Effecrtiveness of Pharmacological Treatments for Preventing Migraine Attacks in Adults 84
Influence of Approaches to Drug Management (Such as Patient Care Teams, Integrated Care, Coordinated Care, Patient Education, Drug Surveillance, or Interactive Drug Monitoring) 85
Comparative Harms From Pharmacological Treatments for Preventing Migraine Attacks in Adults 85
Influence of Patient Characteristics on the Effectiveness and Safety of Pharmacological Treatments for Preventing Migraine Attacks in Adults 86
References 90
Abbreviations 102

Tables

Table 1 Strength of evidence ranks and definitions 6
Table 2. Decrease in migraine frequency by ≥50% with botulinum toxin, pooled results from randomized controlled clinical trials, random effects models with inverse variance weights 28
Table 3. Migraine prevention with topiramate in adults 29
Table 4. Summarizing evidence about migraine prevention with topiramate in adults 30
Table 5. Migraine prevention with divalproex vs. placebo in adults, results from randomized controlled clinical trials 31
Table 6. Migraine prevention with valproate vs. placebo, results from moderate risk of bias randomized controlled clinical trial, (low strength of evidence due to risk of bias and imprecision) 32
Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials 33
Table 8. Reduction in frequency of migraine attack by ≥50% from baseline with timolol 10mg twice a day, attributable events based on meta-analysis of randomized controlled clinical trials 38
Table 9. Efficacy of off-label antiepileptic drugs vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials 39
Table 10. Efficacy of beta blockers for migraine prevention in adults, evidence from randomized controlled clinical trials 40

Table 11. Migraine prevention with antiadrenergics and antidepressant medications, results from randomized controlled clinical trials 41
Table 12. Migraine prevention in adults with calcium channel anatagonists and systemic drug montelukast, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates 43
Table 13. Migraine prevention in adults with angiotensin converting enzyme inhibitors and angiotensin II antagonists, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision 44
Table 14. Migraine prevention in adults with ergot alkaloids, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates 46
Table 15. Migraine prevention in adults with nonsteroid anti-inflammatory drugs, results from randomized controlled clinical trials, low strength of evidence due to risk of bias and imprecision of the estimates 47
Table 16. Comparative effectiveness of topiramate for migraine prevention in adults, individual randomized controlled clinical trials 49
Table 17. Migraine prevention with valproate (600mg/day) vs. cinnarizine (75mg/day) in adults, results from low risk of bias randomized controlled clinical trial, (strength of evidence is low due to imprecision of estimate) 50
Table 18. Comparative effectiveness of beta blockers for migraine prevention in adults 51
Table 19. Comparative effectiveness of antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial 52
Table 20. Comparative effectiveness and safety of beta blockers combined with behavioral therapy (orientation +relaxation training; migraine warning signs and triggers; effectively using migraine medication, and reducing impact of migraines; stress management or biofeedback training; migraine management plan) for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial 53
Table 21. Dose response reduction in migraine attacks by ≥50% from baseline with topiramate in adults 54
Table 22. Adverse effect with botulinum toxin vs. placebo for migraine prevention in adults (magnitude of the effect and strength of evidence from randomized controlled clinical trials) 63
Table 23. Adverse effects with botulinum toxin vs. placebo meta-regression by study level factors (log of relative risk in randomized controlled clinical trials) 64
Table 24. Treatment discontinuation due to adverse effects with topiramate in adults 65
Table 25. Discontinuation due to adverse effects with topiramate in randomized controlled clinical trials of migraine prevention in adults 66
Table 26. Adverse effects with topiramate in adults with migraine, significant results from pooled analysis of randomized controlled clinical trials 67
Table 27. Treatment discontinuation due to bothersome adverse effects and adverse effects with divalproex vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials 68

Table 28. Treatment discontinuation due to bothersome adverse effects with valproate vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trial 70
Table 29. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults, results from randomized controlled clinical trials 71
Table 30. Treatment discontinuation due to bothersome adverse effects with off label antiepileptic drugs vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials (low strength of evidence) 72
Table 31. Treatment discontinuation due to adverse effects with beta blockers for migraine prevention in adults, evidence from randomized controlled clinical trials 73
Table 32. Treatment discontinuation due to adverse effects with antidepressants, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates 74
Table 33. Treatment discontinuation due to adverse effects with ergot alkaloids, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates 75
Table 34. Treatment discontinuation due to any adverse effects with topiramate vs. other drugs for migraine prevention in adults 76
Table 35. Treatment discontinuation due to bothersome adverse effects with Valproate (600 mg/day) vs. cinnarizine (75 mg/day), low strength of evidence from low risk of bias randomized controlled clinical trial 77
Table 36. Comparative safety of beta blockers for migraine prevention in adults, treatment discontinuation due to bothersome adverse effects in randomized controlled clinical trials 78
Table 37. Treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial 79
Table 38. Future research needs 87

Figures

Figure 1. Framework 9
Figure 2. Study Flow 27

Appendixes

Appendix A. Literature Search
Appendix B. Analytical Framework
Appendix C. Excluded Studies
Appendix D. Evidence Tables

Executive Summary

Introduction

According to the International Classification of Headache Disorder, migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours.[1, 2] Migraine headaches range from moderate to very severe[3] and are sometimes debilitating.[4] Migraine affects 17 percent of women and 6 percent of men.[2-5]

Migraine frequency is divided into episodic and chronic.[2] Episodic migraine is characterized by ≤15 and chronic migraine by ≥15 headache days per month. Sometimes migraine may be described as chronic simply because the attacks recur over long periods of time. Chronic migraine affects 8 to13 percent of adults.[8] All migraine types significantly affect the physical, psychological, and social well-being of patients, and can impose serious lifestyle restrictions. Each year lost work time and diminished productivity from migraine costs American employers $225.8 billion.[9-11]

Forty percent of people who experience episodic migraines might benefit from preventive medication;[3, 12, 13] yet, only about 12 percent of adults with frequent migraines take preventive medication.[2, 3, 12, 13] Preventive medications from several drug classes presumably affect various aspects of migraine pathophysiology.[14, 15] The four drugs approved by the U.S. Food and Drug Administration (FDA) for *episodic* migraine prevention in adults include the beta blockers propranolol and timolol, and the antiepileptic drugs topiramate and divalproex sodium.[16] For prevention of *chronic* migraine, the FDA has approved only one drug, botulinum toxin. Doctors also prescribe off-label drugs (approved for clinical conditions other than migraine prevention), including novel antiepileptic drugs, calcium channel modulators, reuptake inhibitors of serotonin and noradrenaline, glutamate blockers, and drugs from several other classes.[16, 17]

Preventive treatments aim to eliminate headache pain.[18-20] Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of ≥50 percent.[6] Preventive treatments are also expected to reduce use of acute drugs and improve quality of life.[3, 21] Treatment safety is defined by the rates of adverse effects that lead to treatment discontinuation. Between 17 and 29 percent of patients discontinue preventive migraine medication because of adverse effects such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness.[22, 23] Drug choices in clinical practice are based on familiarity, efficacy and adverse effects, headache frequency, presence of aura, comorbid conditions, and patient preference.[18, 19, 24-29]

Guidelines differ regarding initiation of preventive treatment. The American Migraine Prevalence and Prevention guideline recommends preventive treatment for those with two or more headache days with disability or four or more days with or without disability.[30] Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month,[1] but others suggest it for those who experience a headache on most days of the month.[24, 31, 32] Often, preventive treatment is recommended for only 6 to 9 months; however, very limited research exists regarding migraine frequency after discontinuation of preventive treatment.[6, 33]

Several gaps remain in the published literature on preventive treatments for migraines. Systematic reviews have focused on the efficacy of specific drugs rather than on the comparative effectiveness of all available pharmacological and nonpharmacological treatments.[34] Little attention has been paid to the comparative effectiveness of off-label drugs to prevent migraine.

Published reviews have not examined quality of life. Clinical reviews have compared the safety of only a few drugs.[34, 35]

Our review focuses on the comparative effectiveness and safety of the drugs for preventing migraine attacks in adults; our results can help inform treatment recommendations. By the nature of the question, our review focuses on outpatient care.

After discussion with key informants,[36] we formulated a list of eligible pharmacological classes. We conducted a comprehensive literature review following the principles in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program[37, 38] and PRISMA guidelines (CRD42012001918).

Key Questions

Question 1

What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults?

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 2

What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?
c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 3

Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?

Methods

Search Strategy

We searched several databases including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database to find original studies published in English up to March 29, 2012. To address grey literature, we searched the FDA Web site to find medical and statistical reviews of the eligible drugs and several trial registries to find ongoing, completed, and published trials of migraine prevention.

Eligibility

Three investigators independently determined study eligibility.[39] To assess the effectiveness of drugs, we analyzed all included randomized controlled trials (RCTs). To assess adverse effects and treatment discontinuation due to adverse effects, we analyzed all included RCTs and nonrandomized studies.[40] We defined harms as the totality of all possible adverse consequences of an intervention.[41] We analyzed harms regardless of how authors perceived causality of treatments.

We defined the target population as community-dwelling adults with episodic or chronic migraine. We defined eligible preventive treatments, outcomes, time, and outpatient setting following the analytical framework (Figure 1). We formulated a list of eligible interventions following discussions with key informants and technical experts, and after consideration of public comments. To assess treatment benefits, we analyzed all RCTs that aimed to examine preventive pharmacological treatments for migraine in community-dwelling adults. Eligible studies included patients with episodic migraine, chronic daily headache, or chronic migraine defined according to the criteria of the International Headache Society.[24] We reviewed RCTs that included adults with migraine, comorbid headache disorders, or tension headache if they examined prevention of migraine. We excluded studies of treatments aimed at acute migraine attacks. We excluded studies that involved patients with other migraine variants, hospitalized patients, and patients in emergency rooms.[42, 43 44] We also excluded studies of short-term prevention of migraine, including menstrual migraines.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies using the criteria from the Cochrane tool for bias in interventional studies.[45] We evaluated (1) random allocation of the subjects to the treatment groups; (2) masking of the treatment status; (3) adequacy of allocation concealment; (4) adequacy of randomization as similarity of the subjects in treatment groups by demographics; frequency and severity of migraine and response to previous treatments; (5) intention-to-treat principles; and (6) selective outcome reporting when compared to the methods sections in the articles. We assumed a low risk of bias when RCTs met all of the risk of bias criteria, a moderate risk of bias if at least one of the risk of bias criteria was not met, and a high risk of bias if two or more risk of bias criteria were not met. We concluded an unknown risk of bias for studies with poorly reported risk of bias criteria. We examined risk of bias in nonrandomized studies according to selection and attrition biases. We evaluated disclosure of conflict of interest by the authors of individual studies and funding sources, but did not use this information to downgrade quality of individual studies.

Grading the Evidence for Each Key Question

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome and for treatment discontinuation due to harms.[46] As part of our strength of evidence assessment we also looked at dose-response association, strength of association, and reporting bias. We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95 percent CIs, and pooled sample had ≥400 events.[47] We did not include justification of the sample size into grading of the evidence nor did we conduct *post hoc* statistical power analysis. We evaluated the strength of the association, defining *a priori* a large effect when relative risk was >2 and a very large effect when relative risk was >5.[39] We defined low magnitude of the effect when relative risk was significant but <2. We defined reporting bias as publication bias, selective outcomes reporting, and multiple publication bias. We did not perform formal statistical tests quantifying the biases.[48]

We defined a high level of evidence on the basis of consistent findings from low risk of bias RCTs. We downgraded strength of evidence to moderate if at least one of the four strength-of-evidence criteria was not met; for example, the studies had moderate risk of bias or the results were not consistent or precise. We downgraded strength of evidence to low if two or more criteria were not met. We defined evidence as insufficient treatment effects or associations were examined by a single study with unclear or high risk of bias.[49] We applied this approach irrespective of statistical significance of the results.

Assessing Applicability

We estimated applicability of the population by evaluating baseline subject characteristics in observational studies and clinical trials.[50]

Data Extraction

Researchers used standardized forms to extract data. We conducted a double independent quality control for the data extracted from RCTs; one reviewer abstracted an article and a second reviewer checked the abstracted data for accuracy. We abstracted the information relevant to the PICOTS framework. We abstracted minimum datasets to reproduce the results presented by the authors. For categorical variables we abstracted the number of events among treatment groups to calculate rates, relative risk, and absolute risk differences. We abstracted means and standard deviations of continuous variables to calculate mean differences with a 95 percent confidence interval (CI).

We abstracted the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We abstracted the time when the outcomes were assessed as weeks from randomization and the time of followup after treatments.

We abstracted inclusion and exclusion criteria, drug regimen and doses, and patient characteristics including demographics, migraine definition, baseline frequency and severity, and prior treatment status as factors that can modify treatment effects. We abstracted sponsorship of the studies, sponsor participation in study design, analysis, and presentation of data, and conflict of interest by the authors.

Data Synthesis

We summarized the results into evidence tables. We focused on patient-centered outcomes, such as reduction in migraine attack rate of ≥50 percent from baseline, quality of life, patient

satisfaction, and composite measures of response including frequency and severity of migraine. We incorporated risk of bias in individual studies into the synthesis of evidence by using individual risk of bias criteria rather than a global score or a ranking category of overall risk of bias.[51, 52]

We synthesized the evidence according to population characteristics that could modify treatment effect, including age, sex, race, and duration of migraine, baseline frequency and severity of acute migraine attacks, presence of aura, previous drug treatments, or history of drug overuse when reported in the original studies. When possible, based on the reporting in original studies, we conducted subgroup and sensitivity analyses according to patient characteristics, drug dose, and timing of followup.

We examined whether the definition of migraine could contribute to differences in trial results. The FDA approved four drugs for prevention of episodic migraine based on trials conducted prior to the recent implementation of the migraine definition proposed by the International Headache Society.[24] Thus, eligible studies published before 2004 defined classic or common migraine as per the Ad Hoc Committee on Classification of Headache.[53]

Using Meta-Analyst[54] and STATA®[55] software at a 95 percent confidence interval, we calculated the relative risk and absolute risk difference from the abstracted events and the mean differences in continuous variables from the reported means and standard deviations. We used correction coefficients and intention to treat as recommended calculations for missing data.[39]

Pooling criteria for Key Questions 1 and 2 included the same active drug treatments and comparators and the same definitions of the outcomes. Standardized mean differences were calculated for different continuous measures of the same outcome. We synthesized sparse data fixed Mantel-Haenszel relative risk, and Peto odds ratio.[56] When studies had no events with active, control, or both treatments, we used correction coefficients and calculated double arcsine transformation for comparing two proportions, and odds ratios from random-effects generalized nonlinear mixed-effect models.[54, 57-60]

We tested consistency in the results by comparing the direction and strength of the association[46] and assessed heterogeneity in results with Chi-square and I-square tests.[61,62] We explored heterogeneity with meta-regression and sensitivity analysis, reporting only the results from random effects models.[63] We used the random effects model to incorporate into the pooled analysis any differences between trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[56] We explored heterogeneity by risk of bias criteria, disclosed conflicts of interest, study sponsorship, dose and duration of drug treatments, time of followup, inclusion of minorities, proportion of women and elderly adults, and other patient characteristics described above. To avoid ecological fallacy, we did not use patient-level variables (for example, mean age or body mass index) in meta-regression.[63]

The number needed to treat to achieve one event of a patient-centered outcome was calculated as reciprocal to absolute risk differences (ARD) in rates of outcome events in the active and control groups.[55, 64] We calculated means and 95 percent CIs for the number needed to treat as reciprocal to pooled ARD when the ARD was significant.[65] The number of avoided or excessive events per population of 1,000 is the difference between the two event rates multiplied by 1,000. We calculated Bayesian odds ratios[54, 60] with 95 percent credible intervals. To conduct indirect comparisons, we used Bayesian network meta-analysis[66] and indirect adjusted frequentist analyses.[67] We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class demonstrated no significant differences in outcomes. We performed all calculations at 95 percent confidence level.

Results

We identified 5,089 references and included 308 references (Figure 2 in the full report). Overall, randomized trials examined 60 drugs from 16 pharmacological drug classes.

We synthesized the evidence of benefits from 183 RCTs published in 207 articles and evidence of harms from the same RCTs and an additional 101 nonrandomized studies. Most RCTs were conducted in the United States and Western countries. Most trials were funded by industry but did not disclose conflict of interest by study investigators. Proportions of industry sponsorship and disclosed conflict of interest varied among examined drugs. More than half of the RCTs had moderate risk of bias, and about a third had low risk of bias. Proportions of low risk of bias RCTs varied among examined drugs.

Applicability of study populations was good. Studies enrolled mostly adults with some adolescents; average age was 35 to 40 years. Middle-aged Caucasian women constituted a majority of the enrollees. Few trials reported the proportion of obese subjects, but many subjects were overweight; the average body mass index was 25.8 kg/m^2.

More than half of the RCTs defined migraine according to the International Headache Society definition. Older publications used the Ad Hoc Committee on Classification of Headache definition of migraine, and about 18 percent of RCTs did not specify a migraine definition. Most trials included patients with and without aura. Enrolled patients had an average of six migraine attacks per month. Most trials excluded patients with severe medical or psychiatric illnesses, stroke, or contraindications to the examined drugs. Due to substantial variability in reporting comorbidities, we could not include this information in quantitative synthesis of evidence. RCTs rarely reported important patient characteristics that could modify drug effects (e.g., family history of migraine, socioeconomic status, response to prior preventive treatments). Loss of followup averaged 13 percent and was the highest with off-label antidepressants.

Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults?

Studies examined four approved drugs for episodic migraine (topiramate, divalproex, propranolol, and timolol), one approved drug for chronic migraine (botulinum toxin), and 55 off-label preventive drugs. Clinically important reduction in episodic migraine frequency by ≥50 percent was examined with 41 different drugs from 13 drug classes, including four approved and 37 off-label drugs. Most trials examined a monotherapy with one active agent compared to placebo or another drug. Treatments lasted an average of 19 weeks (from 4 to 68 weeks). RCTs rarely reported specifics of concomitant treatments such as exact drugs and doses. However, most trials disallowed concomitant drugs during the run-in period and after randomization, thus implying no concomitant treatments were used in the RCTs. Strength of evidence was low due to moderate or high risk of bias and imprecise estimates from individual or meta-analyzed RCTs (Table A).

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?

Prevention of Chronic Migraine

Botulinum toxin was better than placebo in reducing monthly migraine attack by ≥50 percent (Table A).

Prevention of Episodic Migraine

All approved drugs, off-label beta blockers, and angiotensin inhibiting drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent in individual patients (clinical response) (Tables A and B).

Individual RCTs provided low strength of evidence that off-label drugs from different pharmacological classes were effective in reducing monthly migraine frequency by ≥50 percent. Only one off-label drug, captopril, resulted in more than 500 patients showing clinical response attributable to active drugs per 1,000 treated. Other drugs achieved clinical response in 200 to 400 patients per 1,000 treated. In addition to ≥50 percent reduction in monthly migraine frequency, individual RCTs of antiepileptic drugs and beta blockers improved other patient-centered outcomes. Topiramate demonstrated significant improvements in general health status, quality of life, and disability, with score improvements on the Medical Outcome Study Short Form 36 (SF-36) of more than 200 percent for self-reported vitality and more than 100 percent for improvement in pain and general health. Divalproex in a larger dose of 1,500 mg/day increased the likelihood of a 50 percent improvement in whether migraine attacks impaired usual activities or necessitated symptomatic medication and in migraine attacks with nausea, vomiting, phonophobia, or photophobia. Topiramate and propranolol decreased use of drugs for acute migraine attacks.

Antiepileptic drugs carbamazepin and gabapentin were better than placebo in reducing monthly migraine attacks by ≥50 percent. In contrast, carbazepine and acetazolamide failed to prevent migraine attacks.

Beta blockers metoprolol, atenolol, and nadolol but not pindolol were better than placebo in markedly reducing migraine attacks.

Antidepressants amitriptyline, tonabersat, and venlafaxine in a dose of 150 mg/day were better than placebo in reducing monthly migraine attacks by ≥50 percent. In contrast, fluoxetine failed to achieve a self-reported clinical response of “excellent.”

Calcium channel antagonists nimodipine, nicardipine, and verapamil were better than placebo in reducing monthly migraine attacks by ≥50 percent. Rates of complete cessation of migraine were significantly greater with nimodipine than placebo. Verapamil also reduced use of drugs for acute migraine attacks.

Angiotensin converting enzyme inhibitor captopril was examined in adults with comorbid hypertension and depressive symptoms for whom previous antimigraine drugs had been ineffective. Captoptil was better than placebo in achieving complete cessation of migraine and improvement in headache index by ≥50 percent and in reducing depression symptoms. Lisinopril was better than placebo in reducing migraine days and severity of symptoms. It reduced pain measured with SF-36, but did not decrease use of drugs for acute migraine attacks.

Angiotensin II antagonist candesartan was better than placebo in achieving a clinical response defined as ≥50 percent reduction in migraine days, hours, and severity. Candesartan also decreased migraine-related disability but had no effect on use of drugs for acute migraine attacks. In contrast, telmisartan was not better than placebo in reducing monthly migraine attacks by ≥50 percent. Telmisartan reduce the absolute number of migraine days, but had no effect on use of drugs for acute attacks.

Antiadrenergic clonidine was better than placebo in reducing monthly migraine attacks by ≥50 percent. Clonidine reduced use of drugs for acute migraine attacks but did not result in more patients considered better by global assessment. Among other drugs, dihydroergotamine and montelukast were not better than placebo in reducing monthly migraine attacks by ≥50 percent.

b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?

Individual RCTs provided low strength of evidence about the comparative effectiveness of drugs and demonstrated few significant differences (Table C). Indirect adjusted frequentist analysis demonstrated that the angiotensin II receptor antagonist candesartan was more effective than topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline. Network Bayesian meta-analysis demonstrated that angiotensin inhibiting drugs were the most effective for migraine prevention in adults (Table D).

Comparative Effectiveness of Botulinum Toxin on Prevention of Chronic Migraine

Five RCTs provided low strength of evidence about comparative effectiveness of botulinum toxin versus other drugs for chronic migraine prevention in 350 adults ages 18 to 65 with 12 to 24 migraine days per month. Individual RCTs examined the comparative effectiveness of botulinum toxin versus topiramate and found no significant differences in likelihood of migraine prevention or improvement in migraine disability assessment. Absolute scores of the Headache Impact Test were significantly better with topiramate than botulinum toxin; however, need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of botulinum toxin versus divalproex sodium and found no differences in migraine prevention, migraine-related disability, or quality of life between the two drugs.

Comparative Effectiveness of Approved Drugs on Prevention of Episodic Migraine

Individual RCTs provided low strength of evidence that approved antiepileptics and beta blockers were more effective than off-label drugs for migraine prevention (Table C). Topiramate was more effective than amitriptyline or lamotrigine in reducing monthly headache intensity by ≥50 percent. Decrease in headache frequency by ≥50 percent did not differ between topiramate and zonasamide, valproate, levetiracetam, or lamotrigine.

A likelihood of ≥50 percent reduction in monthly migraines and use of the drugs for acute migraine attacks did not differ with topiramate and propranolol. However, topiramate was more effective than propranolol in reducing absolute migraine frequency, duration, and intensity.

Propranolol was more effective than timolol or nifedipine in achieving ≥50 percent reduction of frequency of attacks. A likelihood of ≥50 percent reduction of migraine days did not differ between propranolol and clonidine, propranolol and metoprolol, propranolol and amitriptyline, nortriptyline, or femoxetine. Nadolol at 160 mg/day was more effective than propranolol in increasing the likelihood of clinically important reduction by ≥50 percent in headache frequency, duration, and intensity. Differences between a lower dose of nadolol (80 mg/day) and propranolol (160 mg/day) were not significant.

Comparative Effectiveness of Off-label Drugs on Prevention of Episodic Migraine

Individual head-to-head RCTs provided low strength of evidence about comparative effectiveness of off-label drugs for prevention of episodic migraine.

Double-blind RCTs of *beta blockers* demonstrated no difference in reduction of monthly migraine attacks by ≥50 percent or absolute numbers of migraine days between metoprolol and bisoprolol. Neither did reduction in monthly migraine attacks by ≥50 percent differ between metoprolol and nebivolol. Migraine-related disability, quality of life, and use of acute drugs did not differ with metoprolol and nebivolol. Metoprolol was more effective than aspirin, 300 mg/day, but less effective than aspirin, 1,500 mg/day, in reducing monthly migraine by ≥50 percent. Reduction in monthly migraine attacks by ≥50 percent did not differ between metoprolol and clonidine. However, more patients noticed a reduction in migraine days with metoprolol than clonidine.

Antidepressants fluvoxamine versus amitriptyline or venlafaxine versus amitriptyline demonstrated similar effects on migraine frequency and severity.

Indirect Evidence of Comparative Effectiveness of Preventive Drugs for Episodic Migraine

Network Bayesian meta-analyses demonstrated that ACE inhibitors, angiotensin II antagonists, and off-label beta blockers were the most effective drugs for preventing migraine in adults (Table D). Propranolol, timolol, metoprolol, and atenolol resulted in significantly greater odds of migraine prevention than antiepileptic, antidepressants, and other off-label drugs. All other drugs had similar effectiveness. Indirect adjusted frequentist analysis of 17 effective (better than placebo) drugs demonstrated that the angiotensin II receptor blocker candesartan was more effective than topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline.

c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?

An individual RCT provided low strength of evidence that the likelihood of reducing monthly migraine frequency by ≥25 percent did not differ between propranolol and an intervention consisting of biofeedback-assisted diaphragmatic breathing and systematic relaxation accompanied by home practice of diaphragmatic breathing and systematic relaxation.

d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?

Individual RCTs did not provide sufficient evidence to conclude that combined therapy was more effective than drugs alone.

e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Individual RCTs provided low strength of evidence that increasing the dose of botulinum toxin, topiramate, venlafaxine, pindolol, nadolol, and bisoprolol resulted in a higher response rate. In contrast, higher doses of divalproex, amitriptyline, or propranolol did not result in greater likelihood of clinically important reduction in migraine frequency.

e2. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Six RCTs examined effectiveness of drug management for migraine prevention in 3,825 adults. Four RCTs examined the effectiveness of a multidisciplinary migraine management program and two examined the effectiveness of pharmacist-led drug management (Table E).

Individual RCTs of drug management interventions provided low strength of evidence compared to usual care; multidisciplinary team care improved quality of life and reduced migraine-related disability; a headache management program resulted in complete cessation of migraine; a minimal-contact cognitive-behavioral program improved patient satisfaction with treatments; headache school decreased overuse of drugs for acute headache attacks and reduced migraine disability; pharmaceutical care improved self-efficacy; an intensive pharmaceutical care campaign had no statistically significant impact on use of acute drugs.

Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?

Adverse Effects with Approved Drugs for Chronic Migraine

Botulinum toxin resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo (Table A). In meta-regression, strength of the association was lower in trials with higher placebo rates of adverse effects. Increase in risk of adverse effects was dose responsive. Patients experienced eyelid edema with 50U of botulinum toxin more often than with 7.5 or 25U. Increasing doses of botulinum toxin to 150 to 225U resulted in greater risk of blepharoptosis, muscle weakness, and neck rigidity.

Adverse Effects with Approved Drugs for Episodic Migraine

Bothersome adverse effects leading to treatment discontinuation were examined in 52 RCTs with 28 drugs from eight drug classes. Individual RCTs provided low strength of evidence that topiramate, acetazolamide, and lamotrigine increased rates of treatment discontinuation due to adverse effects more often than placebo. Indirect adjusted frequentist analysis of drugs that caused bothersome adverse effects leading to treatment discontinuation demonstrated no differences between topiramate, amitriptyline, and acetazolamide. Bayesian network meta-analysis demonstrated that topiramate, divalproex, and off-label antiepileptics, antidepressants, and ergot alkaloids increased rates of bothersome adverse effects leading to treatment discontinuation (Table F). Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Topiramate in doses of 100 and 200 mg/day (but not 50 mg/day) resulted in treatment discontinuation due to adverse effects more often than placebo (Table A). Published pooled analysis of individual patient data demonstrated discontinuation of topiramate treatment due to anorexia, anxiety, depression, and hypesthesia. Risk of adverse effects was dose responsive according to the published pooled analyses of individual patient data. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal, dry mouth, marked anorexia, paresthesia or fatigue, mood problems, nausea, and weight loss. Treatment discontinuation due to adverse effects did not differ between divalproex or valproate versus placebo.

Neither propranolol nor timolol caused bothersome adverse effects leading to treatment discontinuation more often than placebo. Timolol did not cause adverse effects more often than placebo.

Adverse Effects with Off-label Drugs for Episodic Migraine

Eight double-blind RCTs examined safety of six off label *antiepileptic drugs* including acetazolamide, gabapentin, vigabatrin, oxcarbazepine, carbamazepin, and lamotrigen. Individual RCTs demonstrated that acetazolamide and lamotrigen resulted in treatment discontinuation due to bothersome adverse effects more often than placebo. Rates of treatment discontinuation due to adverse effects did not differ with placebo compared to carbamazepin, gabapentin, and oxcarbazepine.

Among off-label *beta blockers*, treatment discontinuation due to bothersome adverse effects did not differ with placebo compared to atenolol, bisoprolol, metoprolol, nadolol, or pindolol.

Individual RCTs found no differences in treatment discontinuation due to bothersome adverse effects between placebo and *antidepressants* amitriptyline, femoxetine, fluoxetine, or tonabersat.

Individual RCTs found no differences in treatment discontinuation due to bothersome adverse effects between placebo, lisuride, and methysergide.

b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?

Comparative Harms with Drugs for Prevention of Chronic Migraine

Treatment discontinuation due to adverse effects was less frequent with botulinum toxin than topiramate or amitriptyline (Table C). Botulinum toxin versus divalproex sodium resulted in a higher risk of ptosis.

Comparative Harms with Drugs for Prevention of Episodic Migraine

Individual RCTs provided low strength of evidence about treatment discontinuation due to intolerable adverse effects with specific drugs. Individual RCTs showed that topiramate was better tolerated than amitriptyline in adults with migraine. Treatment discontinuation due to any adverse effects did not differ with topiramate compared to either zonasamide or valproate.

Treatment discontinuation due to exact adverse effects differed between topiramate and other drugs according to individual RCTs. For example, somnolence and weight gain leading to withdrawal was more common with amitriptyline than topiramate. Risk of exact adverse effects also differed between topiramate and other drugs according to individual RCTs. Topiramate increased risk of weight loss when compared to amitriptyline or levetiracetambut but not sodium valproate. Topiramate increased risk of paresthesia when compared to amitriptyline, zonasamide, levetiracetam, or sodium valproate. Risk of dry mouth and constipation was lower with topiramate than amitriptyline.

Treatment discontinuation due to bothersome adverse effects did not differ with propranolol and aspirin or femoxetine. Treatment discontinuation due to bothersome adverse effects did not differ between behavioral migraine management and propranolol or between behavioral migraine management and propranolol in a combined intervention and propranolol alone.

Treatment discontinuation due to adverse effects did not differ between metoprolol versus bisoprolol or nebivolol. Patients experienced moderate adverse effects, fatigue, and bradicarida more often with metoprolol than with nebivolol. Gastrointestinal side effects leading to withdrawal were more common with aspirin than metoprolol. However, total adverse effects and autonomic nervous system and psychiatric disorders were more common with metoprolol than aspirin. Treatment discontinuation due to intolerable adverse effects occurred less often with metoprolol than clomipramine.

Indirect Evidence of Comparative Safety of Drugs for Migraine Prevention in Adults

Bothersome adverse effects leading to treatment discontinuation were examined with 28 different drugs from eight drug classes. Bayesian network meta-analyses demonstrated that topiramate, divalproex, and off-label antiepileptics, antidepressants, and ergot alkaloids resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Table F). Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers. More often than any other examined

drugs, divalproex and off-label antiepileptics led to treatment discontinuation due to bothersome adverse effects.

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

We found no studies that examined adverse effects with drug management interventions.

Question 3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?

Evidence was limited to individual RCTs that examined the drug effect modification by selected patient characteristics.

Baseline Migraine Frequency

Botulinum toxin was more effective in patients with a higher mean baseline migraine frequency according to a single RCT from the BOTULINUM TOXIN North American Episodic Migraine Study Group. Botulinum toxin decreased the likelihood of acute drug use in patients with a baseline of more than 12 monthly migraine days (RR 0.78, 95 percent CI, 0.66 to 0.92).

Amitriptyline was better than placebo in reducing monthly migraine only in patients with >17 migraine attacks per month. Amitriptyline was better than placebo in reducing monthly migraine only in depressed patients with baseline frequent and severe migraine. A higher dose of amitriptyline increased the odds of reducing monthly migraine by ≥50 percent, and the response increased in association with increased baseline migraine days (odds ratio 2.4, 95 percent CI, 1.45 to 3.8 for every additional day of migraine at baseline).

Concurrent Prophylactic Medication Use

Botulinum toxin more often than placebo led to adverse effects, blepharoptosis, muscle weakness, and neck pain, irrespective of concurrent prophylactic medication use, according to the BOTULINUM TOXIN CDH Study Group.

Sex

Topiramate caused a complete cessation of migraine attacks in women but not in men according to a low risk of bias RCT. Per 1,000 women treated, topiramate caused a complete cessation of migraine attacks in 37 (95 percent CI, 8 to 67) and a reduction of monthly migraine attacks by ≥50 percent in 249 (95 percent CI, 178 to 320). However, men experienced a reduction of monthly migraine 75 to 90 percent more often with topiramate than with placebo.

Presence of Aura

Gabapentin reduced migraine attack frequency and intensity significantly more than placebo irrespective of the presence of aura. Patients with aura experienced slightly greater reduction in migraine frequency (mean difference -2.2, 95 percent CI, -2.7 to -1.7) than patients without aura (mean difference -1.6, 95 percent CI, -2.2 to -0.9). Patients with aura experienced slightly greater

reduction in migraine intensity (mean difference-0.83, 95 percent CI, -1.12 to-0.54) than patients without aura (mean difference -0.42, 95 percent CI, -0.77 to -0.07).

Discussion

All approved drugs, off-label beta blockers, and angiotensin acting drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response). The relative effect size of drugs was moderate: drugs resulted in to 200 to 400 cases of clinical response (≥50 percent reduction in monthly migraine frequency) per 1,000 treated.

Critical assessment of the strength of the available evidence suggested low risk of bias in one third of included RCTs and moderate risk of bias in more than half of included RCTs. Strength of evidence was high only for topiramate, moderate for timolol and metoprolol, and low for other drugs due to risk of bias and imprecise estimates. Many authors of individual trials did not provide sufficient details about allocation concealment methods or about planned measurements of clinically important changes in quality of life scores and did not use intention-to-treat principles for all examined outcomes. We incorporated risk of bias in our evaluation of strength of evidence, but we could not estimate the effect of risk of bias criteria on drug benefits or safety because most evidence came from individual RCTs. The role of financial conflict of interest and industry sponsor participation in data analyses and interpretation was difficult to evaluate because of inconsistent reporting and insufficient detail from individual studies.[68] For instance, the same authors disclosed no or different relationships with industry in multiple publications. Subjects' baseline severity and frequency of migraine attacks as well as comorbidities and concomitant treatments were inconsistently reported.[6, 69]

Applicability of the studies' population was good since trials enrolled predominantly middle-aged Caucasian women. However, average treatment effects in a clinically diverse population may not reflect the actual effects for a specific subgroup.[70] Very few studies provided evidence for individualized treatment decisions with clear descriptions of planned stratified randomization and subgroup analyses. Published RCTs rarely reported important patient characteristics that could modify drug effects (family history of migraine, socioeconomic status, or a response to prior preventive treatments).[21, 71] No trials examined the role of genetic polymorphism in drug metabolism and effects.[72-74]

Few RCTs reported treatment effects in patient subpopulations. Low strength of evidence suggested that botulinum toxin[75] and amitriptyline[76] were more effective in patients with frequent baseline migraine. Rates of migraine prevention varied from 1 to 50 percent in examined RCTs. Our review demonstrated that a relative risk of adverse effects with botulinum toxin was lower in trials with higher placebo rates of adverse effects.[77] Previous research demonstrated that compared to patients with epilepsy, patients with migraine more often quit taking topiramate due to bothersome adverse effects.[23] Most trials in our review excluded patients with severe medical or psychiatric illnesses, stroke, and vascular migraine. Substantial variability in reporting comorbidities prevented us from using this information in quantitative synthesis of evidence.

Comparative effectiveness and safety with preventive drugs were examined in individual RCTs that failed to meet pooling criteria. Variability in examined drug comparisons in head-to-head RCTs precluded meta-analysis of direct evidence. However, because we found no differences across RCTs in baseline patient characteristics, indirect comparisons were feasible. Thus, we conducted Bayesian network meta-analyses, which indicated that angiotensin acting drugs and beta blockers were the most effective and safe drugs. Head-to-head trials were not

designed to test safety with migraine preventive drugs. Very few trials demonstrated significant increase in rates of bothersome adverse effects leading to treatment discontinuation when compared to placebo. In contrast, network meta-analysis demonstrated that patients stopped taking drugs more often than placebo with topiramate, divalproex, off-label antiepileptics, antidepressants, and ergot alkaloids.

Average rates of treatment discontinuation due to bothersome adverse effects were 6 percent with placebo, 6 percent with propranolol, and 4 percent with off-label beta blockers. In contrast, 15 percent of patients stopped taking topiramate, 12 percent stopped taking divalproex, 12 percent stopped taking antidepressants, and 10 percent stopped taking an off-label antiepileptic. Individual adverse effects varied depending on the pharmacodynamic properties of the drugs. Multidisciplinary drug management programs demonstrated improvement in migraine related disability and patient satisfaction, but long-term adherence and benefits are unclear.

The few RCTs that examined quality of life provided no consistent evidence of improvement with examined drugs. The authors rarely measured quality of life using the disease specific Migraine Specific Questionnaire, Migraine Disability Assessment, or the Headache Impact Test. We could not determine the clinical importance of statistically different changes in scores.

Our review has implications for clinical practice. Informed decisions in clinical settings should take into account the rates of benefits and harms attributable to specific drugs.[78]

The most effective and safest drugs should be the first choice in adult migraine prevention. Our review demonstrated that approved beta blockers along with off-label beta blockers and angiotensin acting drugs have better benefits and harms profiles than other drugs examined in RCTs in adults who have episodic migraine and no contraindications to examined drugs. We found no published controlled observational studies about preventive drug use and comparative effectiveness of approved versus off-label drugs.

Some evidence suggests that off-label drug use is common in the United States, with little or no scientific support.[17] For instance, the Institute for Healthcare Informatics Health National Disease and Therapeutic Index analysis suggested that 20 percent of all outpatient drug prescriptions for adults were for off-label drugs, with the most common being anticonvulsants (46 percent), gabapentin (83 percent), and amitriptyline hydrochloride (81 percent).[79] We found that off-label antiepileptic and antidepressants demonstrated worse benefits and safety profiles than beta blockers or angiotensin acting drugs. Evidence of off-label drug use and associated adverse effects has been evaluated with prospective pharmacovigilance surveys in European countries.[80,81] Routine monitoring of harms with off-label drugs via collecting and analyzing comparative safety evidence in clinical settings is needed in the United States.

Our report has limitations. First, we acknowledge possible reporting bias in complete outcomes availability from all conducted studies. We restricted our review to studies published in English in journals, reviewed by the FDA, or reported on the ClinicalTrials.gov Web site. Even after such a comprehensive review of evidence, we do not know how many funded but unregistered studies we may have missed in our review. Published articles rarely provided unique trial registration numbers from Clinicaltrials.gov. We concluded multiple reports of the same data based on available information and did not contact the authors for further clarification. We suspected selective harms reporting because published articles reported common and expected adverse effects. In contrast, few RCTs that posted the results in Clinicaltrials.gov reported all harms irrespective of rate or assumed association with active drugs. We did not contact the authors requesting unreported benefits and harms. In cases of poor reporting of risk of bias criteria, we did not contact the authors for additional details about methodological

quality. Vast variability in examined treatment options, risk of bias, and imprecise estimates from small individual RCTs hampered synthesis of evidence. We found no evidence of baseline differences in enrolled populations by age, proportion of women, and baseline frequency of migraine. We used indirect network meta-analysis to synthesize treatment effects of several pharmacological classes. However, indirect comparisons did not address unreported baseline differences in comorbidities or in socioeconomic status.

We did not grade strength of evidence for flunarizine, a drug widely used in other countries, because the FDA has not approved it. According to our analyses of 26 RCTs, flunarizine was not better than placebo in reducing monthly migraine attacks by ≥50 percent or in reducing use of acute drugs.

We identified gaps and biases in available evidence that should direct future research. Randomized well-designed clinical trials should examine the comparative effectiveness of the approved drugs and the most effective off-label ACE inhibitors, angiotensin II blockers, and off-label beta blockers. Future trials should examine the role of patient age, gender, race, migraine family history, comorbidities, and prior treatment response in modifying benefits and harms with migraine preventive drugs. Observational studies should analyze off-label drug utilization and comparative effectiveness and safety with migraine preventive drugs. Analysis of administrative databases should examine emergency and doctor visits among adults taking migraine preventive drugs. Prospective pharmacovigilance methods should be used for routine monitoring of off-label drug use and associated adverse effects with migraine preventive drugs.

Our review provides a comprehensive network analysis of comparative effectiveness and harms with migraine preventive drugs in adults. We concluded that angiotensin inhibiting drugs demonstrated the most effective migraine prevention without bothersome adverse effects leading to treatment discontinuation. All approved drugs (botulinum toxin, topiramate, divalproex, timolol, and propranolol) and off-label beta blockers were better than placebo in reducing monthly migraine frequency by ≥50 percent. However, topiramate, divalproex, and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.

Our review identified gaps in evidence and directions for future research. Long-term preventive benefits and adherence with drugs are unknown. Evidence on improving quality of life was inconsistent across individual drugs. Evidence for individualized treatment decisions is very limited. Future research is needed for identifying the role of patient characteristics on long-term drug benefits and safety.

Key Messages

Efficacy and Comparative Effectiveness of Pharmacological Treatments for Preventing Migraine Attacks in Adults

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Placebo or No Active Treatment

- All approved drugs, off-label beta blockers, and ACE inhibitors were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response).
- Relative effect of drugs was moderate: drugs resulted in clinical response in 200 to 400 patients per 1,000 treated.

- Only one off-label drug, captopril, resulted in an attributable clinical response in more than 500 patients per 1,000 treated.
- Strength of evidence was high for topiramate, moderate for timolol and metoprolol, and low for other drugs due to moderate risk of bias and imprecise estimates.
- Low strength of evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of botulinum toxin, topiramate (from 50-100 mg with no additional benefits with 200 mg/day), pindolol, nadolol, bisoprolol, and venlafaxine.

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Active Pharmacological Treatments

- Individual RCTs provided low strength of direct evidence about the comparative effectiveness of drugs and demonstrated few significant differences.
- Network Bayesian meta-analysis of 84 RCTs with 41 different drugs from 13 drug classes demonstrated that ACE inhibitors, angiotensin II receptor antagonists, propranolol, and off-label beta blockers are more effective than all other drugs.

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Active Nonpharmacological Treatments

- Individual RCTs provided low strength of evidence a ≥50 percent reduction in monthly migraine attacks did not differ with propranolol versus biofeedback or amitriptyline versus spinal manipulation.

Influence of Approaches to Drug Management (Such as Patient Care Teams, Integrated Care, Coordinated Care, Patient Education, Drug Surveillance, or Interactive Drug Monitoring)

- Multidisciplinary team care improved quality of life and reduced migraine-related disability.
- Headache management program resulted in complete cessation of migraine.
- A cognitive-behavioral minimal contact program improved patient satisfaction with treatments.
- Headache school decreased overuse of acute drugs and reduced migraine disability.
- An intensive pharmaceutical care campaign had no statistically significant impact on use of drugs for acute attacks.

Comparative Harms From Pharmacological Treatments for Preventing Migraine Attacks in Adults

- Bothersome adverse effects leading to treatment discontinuation were examined in 52 RCTs with 28 different drugs from eight drug classes.
- Moderate strength of evidence suggested that topiramate and botulinum toxin resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- The association was dose responsive for topiramate.

- Among other drugs, acetazolamide and lamotrigine resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- Limited low strength evidence from individual head-to-head RCTs suggested that propranolol was safer than nifedipine and metoprolol was safer than clomipramine in regard to causing intolerable adverse effects.
- Bayesian network meta-analysis suggested that topiramate, divalproex, off-label antiepileptic, antidepressants, and ergot alkaloids increased the rates of bothersome adverse effects leading to treatment discontinuation.
- Divalproex and the off-label antiepileptic resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Influence of Patient Characteristics on the Effectiveness and Safety of Pharmacological Treatments for Preventing Migraine Attacks in Adults

- Evidence was limited to individual RCTs that examined the drug effect modification by selected patient characteristics.
- Botulinum toxin was more effective in patients with a higher mean baseline migraine frequency.
- Amitriptyline was better than placebo in reducing monthly migraine only in patients with >17 migraine attacks per month and in depressed patients with baseline severe migraine.

Table A. Efficacy and safety of migraine preventive pharmacological treatments, evidence from meta-analyzed randomized controlled clinical trials

Outcome	Active vs. control preventive treatment	Sample	Rate, percent with drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence Reasons for lowering SOE
≥50% decrease in migraine frequency	Botulinum toxin vs. placebo	459	50.6 [34.4]	1.5 (1.2 to 1.8)	0.17 (0.08 to 0.26)	6 (4 to 12)	170 (82 to 258)	Low (moderate ROB, imprecision)
Discontinuations related to adverse effect	Botulinum toxin vs. placebo	1384	3.8 [1.1]	3.2 (1.4 to 7.1)	0.03 (0.01 to 0.04)	38 (23 to 100)	26 (10 to 43)	Moderate (moderate ROB)
≥50% reduction in monthly migraine days	Topiramate 50 to 200mg/day vs. placebo	1,145	41.8 [22.8]	1.8 (1.1 to 2.9)	0.18 (0.08 to 0.28)	5 (4 to 11)	182 (93 to 271)	High
≥75% decrease in migraine frequency	Topiramate 50 to 200mg/day vs. placebo	1,327	21.2 [9.9]	2.1 (1.6 to 2.8)	0.12 (0.02 to 0.22)	7 (4 to 48)	142 (21 to 262)	High
≥75% reduction in monthly migraine days	Topiramate vs. placebo	328	15.2 [9.2]	2.1 (1.6 to 2.9)	0.11 (0.02 to 0.19)	10 (6 to 27)	105 (37 to 173)	Moderate (imprecision)
≥50% decrease in migraine frequency	Topiramate 100 mg/day vs. placebo	774	44.1 [21.7]	2.0 (1.3 to 3.2)	0.26 (0.07 to 0.44)	4 (3 to 10)	250 (104 to 396)	High
≥50% decrease in migraine frequency	Topiramate 200mg/day vs. placebo	746	46.4 [24.2]	2.0 (1.3 to 3.0)	0.23 (0.12 to 0.33)	4 (3 to 8)	224 (123 to 325)	High
≥50% decrease in migraine frequency	Topiramate 50mg/day vs. placebo	507	37.9 [21.2]	1.7 (1.2 to 2.6)	0.23 (0.06 to 0.41)	4 (2 to 22)	244 (46 to 441)	High
Complete cure	Topiramate 50 to 200mg/day vs. placebo	893	5.2 [1.7]	2.2 (0.9 to 5.5)	0.03 (-0.02 to 0.07)	Not significant	Not significant	Moderate (imprecision)
Discontinued due to adverse events	Topiramate 100 mg/day vs. placebo	1719	12.6 [6.2]	1.6 (1.1 to 2.2)	0.04 (0.01 to 0.06)	28 (17 to 71)	36 (14 to 58)	Moderate (moderate ROB)
Discontinued due to adverse events	Topiramate 200 mg/day vs. placebo	586	22.2 [6.6]	2.6 (1.5 to 4.6)	0.15 (0.07 to 0.22)	7 (4 to 15)	146 (68 to 223)	Low (moderate ROB, imprecision)
Discontinuations due to adverse events	Topiramate 50 mg/day vs. placebo	310	17.5 [10.8]	1.5 (0.7 to 2.9)	0.06 (-0.03 to 0.15)	Not significant	Not significant	Low (moderate ROB, imprecision)

Table A. Efficacy and safety of migraine preventive pharmacological treatments, evidence from meta-analyzed randomized controlled clinical trials (continued)

Outcome	Active vs. control preventive treatment	Sample	Rate, percent with drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence Reasons for lowering SOE
≥50% decrease in migraine frequency	Divalproex vs. placebo	346	43.0 [24.2]	2.1 (0.9 to 4.7)	0.23 (0.03 to 0.43)	4 (2 to 40)	226 (25 to 427)	Low (moderate ROB, imprecision)
Discontinuations due to adverse effects	Divalproex mean dose 871-1087 vs. placebo	346	9.8 [7.8]	1.2 (0.5 to 2.7)	0.02 (-0.05 to 0.10)	Not significant	Not significant	Low (moderate ROB, imprecision)
≥50% decrease in migraine frequency	Propranololvs. placebo	559	45.5 [21.0]	2.0 (1.5 to 2.7)	0.26 (0.16 to 0.35)	4 (3 to 6)	256 (158 to 353)	Low (moderate ROB, imprecision)
≥50% decrease in migraine frequency	Timolol vs. placebo	276	49.4 [23]	2.1 (1.5 to 3.1)	0.3 (0.2 to 0.4)	4 (3 to 6)	265 (154 to 377)	Moderate (moderate ROB)
≥50% decrease in migraine frequency	Metoprolol vs. placebo	291	39.9 [19.4]	2.0 (1.3 to 3.2)	0.20 (0.09 to 0.3)	5 (3 to 11)	204 (88 to 321)	Moderate (moderate ROB)
≥50% decrease in migraine frequency	Propranolol vs. metoprolol	113	38.2 [50.0]	0.8 (0.5 to 1.2)	-0.12 (-0.30 to 0.06)	Not significant	Not significant	Low (moderate ROB, imprecision)
≥50% decrease in migraine frequency	Timolol vs. propranolol	242	47.9 [50.4]	1.0 (0.7 to 1.2)	-0.03 (-0.15 to 0.10)	Not significant	Not significant	Low (moderate ROB, imprecision)
≥50% decrease in migraine frequency	Propranolol vs. Nifedipine	76	46.2 [18.9]	2.3 (1.1 to 4.6)	0.27 (0.09 to 0.46)	4 (2 to 11)	274 (89 to 458)	Low (high ROB, imprecision)

SOE – strength of evidence; ROB – risk of bias

Table B. Evidence map for efficacy and safety of migraine preventive pharmacological treatments (show if reported in more than one study)

Active treatment vs. placebo	# of RCTs/sample size Treatment response Strength of evidence	# of RCTs/sample size Treatment discontinuation due to adverse effects Strength of evidence	# of RCTs/sample size Quality of life Strength of evidence	Conclusion
Botulinum toxin	3/459 Improvement Low	2/1384 Increase Moderate	Inconsistent in individual RCTs Insufficient	Botulinum toxin was better than placebo in preventing migraine but resulted in bothersome adverse effects leading to treatment discontinuation.
Topiramate 50 to 200mg/day	Complete cure 4/893 Not significant Moderate	Not available from RCTs	Not available from RCTs	Topiramate was not better than placebo in achieving complete cure from migraine attacks.
Topiramate 50mg/day	4/507 Improvement High	2/310 Not significant Low	Not available from RCTs	Topiramate, 50 mg/day was better than placebo in achieving ≥50% reduction in monthly migraine frequency and did not result in treatment discontinuation due to bothersome adverse effects.
Topiramate 100 mg/day	4/774 Improvement High	7/1719 Increase Moderate	1/328 Improvement Low	Topiramate, 100 mg/day was better than placebo in achieving ≥50% reduction in monthly migraine frequency but also led to treatment discontinuation due to adverse effect.
Topiramate 200mg/day	5/746 Improvement High	4/586 Increase Low	Significant improvement in individual RCTs Low	Topiramate, 200 mg/day was better than placebo in achieving ≥50% reduction in monthly migraine frequency but also led to treatment discontinuation due to adverse effect.
Topiramate, dose response	200mg vs. 50 mg 3/526 Improvement 200mg/day vs. 100mg/day 3/526 Not significant	2/365 Not significant	Not available from RCTs	Increase in topiramate dose to 100 mg/day resulted in higher response rate without additional benefit from increasing the dose to 200 mg/day.
Divalproex sodium	2/346 Improvement Low	2/346 Not significant Low	Not available from RCTs	Divalproex was better than placebo in preventing migraine and did not increase rates of treatment discontinuation due to bothersome adverse effects.
Timolol	3/276 Improvement Moderate	1/94 Not significant Low	Not available from RCTs	Timolol was better than placebo in preventing migraine and did not result in bothersome adverse effects leading to treatment discontinuation.
Propranolol	5/560 Improvement Low	1/166 Not significant Low	Not available from RCTs	Propranolol was better than placebo in preventing migraine and did not increase rates of treatment discontinuation due to bothersome adverse effects.
Amitriptyline	Improvement in composite score ≥50% 1/116 Improvement Low	2/507 Not significant Low	Not available from RCTs	Amitriptyline was better than placebo in improving composite score and did not result in treatment discontinuation due to bothersome adverse effects.

Table C. Comparative effectiveness and safety with migraine preventive drugs in adults, direct evidence from head-to-head randomized controlled clinical trials

Treatment comparison	# of RCTs/sample size Treatment response Strength of evidence	# of RCTs/sample size Treatment discontinuation due to adverse effects Strength of evidence	Conclusion
Topiramate 100 mg/d vs. propranolol	1/285 Not significant Low	Not available from RCTs	Topiramate, 100mg, and propranolol did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Topiramate 200 mg/d vs. propranolol	1/288 Not significant Low	Not available from RCTs	Topiramate, 200 mg, and propranolol did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Divalproex vs. propranolol	1/74 Not significant Insufficient	1/74 Not significant Insufficient	Divalproex and propranolol did not differ in migraine prevention or bothersome adverse effects leading to treatment discontinuation.
Propranolol vs. clonidine	1/46 Not significant Low	Not available from RCTs	Propranolol and clonidine did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Propranolol vs. metoprolol	2/113 Not significant Low	Not available from RCTs	Propranolol and metoprolol did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Propranolol vs. nadolol	1/91 **Worse effect** Low	Not available from RCTs	Propranolol was less effective than nadolol in preventing migraine. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Timolol vs. propranolol	2/242 Not significant Low	Not available from RCTs	Timolol and propranolol did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment discontinuation was not examined.
Propranolol vs. nifedipine	2/76 **Improvement** Low	1/40 **Better Safety** Insufficient	Propranolol was more effective and safe than nifedipine.
Propranolol vs. nortriptyline	1/49 Not significant Low	Not available from RCTs	Propranolol and nortriptyline did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment.
Propranolol vs. amitriptyline	1/108 Not significant Low	Not available from RCTs	Propranolol and amitriptyline did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment.

Table C. Comparative effectiveness and safety with migraine preventive drugs in adults, direct evidence from head-to-head randomized controlled clinical trials (continued)

Treatment comparison	# of RCTs/sample size Treatment response Strength of evidence	# of RCTs/sample size Treatment discontinuation due to adverse effects Strength of evidence	Conclusion
Propranolol vs. femoxetine	1/29 Not significant Low	Not available from RCTs	Propranolol and femoxetine did not differ in migraine prevention. Comparative safety on bothersome adverse effects leading to treatment.
Lisuride vs. methysergide	1/253 Not significant Low	1/253 **Better Safety** Low	Lisuride and methysergide did not differ in migraine prevention. Lisuride resulted in less rates of treatment discontinuation due to bothersome adverse effects.
Behavioral migraine management vs. behavioral migraine management + propranolol/nadolol	1/124 **Worse effect** Low	1/124 Not significant Low	Combined behavioral migraine management + propranolol/nadolol treatment was more effective than behavioral migraine management alone with no differences in treatment discontinuation due to bothersome adverse effects.
Clomipramine vs. metoprolol	Not available from RCTs	1/126 **Increase** Low	Comparative effectiveness of clomipramine vs. metoprolol on ≥50% reduction in monthly migraine attack was not examined. Metoprolol results in lower rated of treatment discontinuation due to adverse effects.
Metoprolol vs. bisoprolol	1/230 Not significant Low	1/156 Not significant Low	Comparative effectiveness of metoprolol vs. bisoprolol on ≥50% reduction in monthly migraine attack was not examined. Treatment discontinuation due to bothersome adverse effects did not differ with two drugs.
Metoprolol vs. nebivolol	1/30 Not significant Low	1/30 Not significant Low	Comparative effectiveness of metoprolol vs. nebivolol on ≥50% reduction in monthly migraine attack was not examined. Treatment discontinuation due to bothersome adverse effects did not differ with two drugs.

Bold – significant effects of drugs on treatment response and discontinuation due to adverse effects when 95% CI of attributable events per 1000 treated do not include 0.

Table D. Odds ratios from network Bayesian meta-analysis of clinically important (≥50%) reduction in migraine with preventive drugs in adults, results from randomized controlled clinical trials (84 RCTs with 41 different drugs)

Control / Active	Placebo	Topiramate	Valproate or divalproex	Propranolol	ACE inhibitors or angiotensin blockers	Off-label beta blockers	Anti-depressants	Off label antiepileptics	Ergot alkaloids
Topiramate	**2.9 (1.9;4.5)**								
Valproate or divalproex	**3.4 (1.7;7.0)**	1.2 (0.5;2.6)							
Propranolol	**3.5 (2.2;5.8)**	1.2 (0.7;2.2)	1.0 (0.5;2.2)						
ACE inhibitors or angiotensin blockers	**17.3 (6.2;58.9)**	**6.0 (2.0;21.4)**	**5.2 (1.5;20.9)**	**4.9 (1.6;17.5)**					
Off-label beta blockers	**4.8 (2.9;8.3)**	1.7 (0.9;3.2)	1.4 (0.6;3.3)	1.4 (0.8;2.4)	**0.3 (0.1;0.9)**				
Antidepressants	**2.9 (1.5;5.6)**	1.0 (0.5;2.0)	0.8 (0.3;2.1)	0.8 (0.4;1.6)	**0.2 (0.0;0.6)**	0.6 (0.3;1.3)			
Off-label antiepileptics	**2.3 (1.2;4.4)**	0.8 (0.4;1.6)	0.7 (0.3;1.8)	0.6 (0.3;1.4)	**0.1 (0.0;0.4)**	0.5 (0.2;1.1)	0.8 (0.3;1.9)		
Ergot alkaloids	1.2 (0.3;5.7)	0.4 (0.1;2.1)	0.4 (0.1;2.0)	0.3 (0.1;1.7)	**0.1 (0.0;0.4)**	0.3 (0.1;1.3)	0.4 (0.1;2.2)	0.5 (0.1;2.9)	
Other off-label drugs	**3.3 (2.0;5.7)**	1.1 (0.6;2.1)	1.0 (0.4;2.1)	0.9 (0.5;1.6)	**0.2 (0.1;0.6)**	0.7 (0.4;1.2)	1.2 (0.5;2.5)	1.4 (0.7;3.2)	2.7 (0.5;13.9)

Bold - significant effects of drugs when 95% CI of odds ratios do not include 1.

Table E. Prevention of migraine with drug management programs, results from individual randomized controlled clinical trials

Reference Treatment vs. control Sample, Risk of bias	Description	Results
Lemstra, 2002 Multidisciplinary intervention vs. standard medical care with the patient's family physician Sample: 80 Risk of bias moderate	Multidisciplinary intervention: It consisted of a neurologist intake, physical therapist intake, 18 group-supervised exercise therapy sessions with an exercise therapist, 2 group lectures with a registered psychologist 1 group lecture with a dietitian, 2 massage therapy sessions, and a neurologist and physical therapist.	More effective in improving quality of life and reducing migraine related disability with no statistically significant changes in the use of acute drugs or work status.
Matchar, 2008 Headache management program vs. continue with current clinician Sample: 614 Risk of bias moderate	Headache management program consisting of :1) a class specifically designed to inform patients about headache types, triggers, and treatment options; 2) diagnosis and treatment by a professional especially trained in headache care (based on US Headache Consortium guidelines); and 3) proactive follow-up by a case-manager.	More effective in improving quality of life and satisfaction with care; 196 adults per 1,000 treated (95 percent CI, 125 to 258) had no migraine-related disability with the headache management program.
Fritsche, 2010 Cognitive-behavioral minimal contact program (MCT) vs. two brochures Sample: 158 Risk of bias Low	It consisted of 5 sessions with sic participants and lasting 2 hours each: "Introduction and syndrome education" ; "Medication rules and the risk of Medication Overuse Headache" including information about prophylactic migraine medication and medication overuse; "Medication intake behavior" aimed at raising awareness for "external" and "internal" influences on patient's medication intake behavior;"General and personal risk factors for drug intake"; "Everyday transfer aimed to establishing individual goals for future drug intake and learning how to make use of social support to control intake behavior.	More effective in patient satisfaction. No effects on migraine frequency or duration of migraine related disability, social activity engagement, pain self-management, or migraine related anxiety and depression.
Rothrock, 2006 Standardized course of didactic instructions regarding migraine biogenesis and management ("headache school") Sample: 100 Risk of bias moderate	The curriculum consisted of 3 90-minute classes held on evenings and weekends and taught by lay migraineurs who previously had undergone intensive classroom and in-clinic training by neurology investigators. All individuals serving as patient instructors underwent 12 hours of classroom instruction in headache theory and treatment, received and reviewed a related course syllabus, were required to pass successfully a written examination based on that didactic instruction, and then served a minimum of 12 hours as observers in the headache clinics.	Decreased overuse of acute drugs and reduced migraine disability.
Hoffmann, 2008 Pharmaceutical care for migraine vs. regular pharmaceutical consultation Sample: 410 Risk of bias low	Pharmacists from the intervention pharmacies participated in a 2-day central training program conducted by a physician and a pharmacist. Together with the patient, the intervention pharmacist prioritized problems, defined goals, and devised a plan to work toward them. The training was based on a comprehensive standard operation manual developed by the Federal Union of German Associations of Pharmacists, in cooperation with the principal.	Complete migraine cessation did not differ between active and control intervention.
Sondergaard, 2006 Intensive pharmaceutical care campaign Sample: 2463 Risk of bias low	Pharmacists from the intervention pharmacies identified inappropriate triptan use, established a dialogue with individual patients and offered advice about migraine management with preventive drugs to reduce triptan overuse. The training package was developed in cooperation with the Danish College of Pharmacy Practice.	Significant improvement in mental health and self-efficacy; no statistically significant impact on use of triptans.

Table F. Odds ratios from network Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (52 RCTs with 28 different drugs)

Control / Active	Placebo	Topiramate	Valproate	Propranolol	Divalproex	Off label beta blockers	Antidepressants	Off label antiepileptics
Topiramate	**2.2 (1.5;3.4)**							
Valproate	2.0 (0.3;12.8)	1.0 (0.1;6.0)						
Propranolol	1.5 (0.6;3.5)	0.7 (0.3;1.7)	0. (0.1;5.1)					
Divalproex	**4.2 (1.0;21.7)**	1.9 (0.4;10.4)	2.0 (0.2;24.6)	2.8 (0.7;15.3)				
Off-label beta blockers	0.5 (0.2;1.1)	0.2 (0.1;0.6)	0.2 (0.0;1.8)	**0.3 (0.1;0.9)**	**0.1 (0.0;0.6)**			
Antidepressants	**2.5 (1.5;4.5)**	1.2 (0.6;2.1)	1.2 (0.2;8.2)	1.8 (0.7;4.4)	0.6 (0.1;2.8)	**5.2 (2.1;13.1)**		
Off-label antiepileptics	**1.8 (1.0;3.4)**	0.8 (0.4;1.6)	0.9 (0.1;6.3)	1.3 (0.4;3.6)	0.4 (0.1;2.1)	**3.7 (1.4;10.2)**	0.7 (0.3;1.6)	
Other off-label drugs	**3.9 (1.8;9.5)**	1.8 (0.7;4.6)	1.9 (0.3;12.2)	**2.8 (1.1;7.1)**	0.9 (0.2;4.7)	**8.1 (2.9;26.2)**	1.6 (0.7;3.9)	2.2 (0.8;6.3)

Bold - significant effects of drugs when 95% CI of odds ratios do not include 1.

Glossary

AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
CI	Confidence interval
FDA	Food and Drug Administration
PICOTS	Population(s), Intervention, Comparators, Outcomes, Timing, Settings
RCT	Randomized controlled trial

References

1. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
2. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007 Mar;47(3):355-63. PMID: 17371352.
3. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002 Mar 26;58(6):885-94. PMID: 11914403.
4. Bigal ME, Lipton RB, Winner P, et al. Migraine in adolescents: association with socioeconomic status and family history. Neurology. 2007 Jul 3;69(1):16-25. PMID: 17606878.
5. Hernandez-Latorre MA, Roig M. Natural history of migraine in childhood. Cephalalgia. 2000 Jul;20(6):573-9. PMID: 11075841.
6. Silberstein SD. Preventive migraine treatment. Neurol Clin. 2009 May;27(2):429-43. PMID: 19289224.
7. Solomon GD, Santanello N. Impact of migraine and migraine therapy on productivity and quality of life. Neurology. 2000;55(9 Suppl 2):S29-35. PMID: 11089517.
8. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010 May;30(5):599-609. PMID: 19614702.
9. Stewart WF, Ricci JA, Chee E, et al. Lost productive work time costs from health conditions in the United States: results from the American Productivity Audit. J Occup Environ Med. 2003 Dec;45(12):1234-46. PMID: 14665809.
10. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. Arch Intern Med. 1999 Apr 26;159(8):813-8. PMID: 10219926.
11. Burton WN, Landy SH, Downs KE, et al. The impact of migraine and the effect of migraine treatment on workplace productivity in the United States and suggestions for future research. Mayo Clin Proc. 2009 May;84(5):436-45. PMID: 19411440.
12. Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. Neurology. 2003 Feb 11;60(3):441-8. PMID: 12578925.
13. Lipton RB, Stewart WF. The epidemiology of migraine. Eur Neurol. 1994;34 Suppl 2:6-11. PMID: 7835383.
14. Sprenger T, Goadsby PJ. Migraine pathogenesis and state of pharmacological treatment options. BMC Medicine. 2009;7:71. PMID: 19917094.
15. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. Curr Opin Neurol. 2006 Jun;19(3):294-8. PMID: 16702838.
16. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. Neurol Sci. 2008 May;29 Suppl 1:S110-22. PMID: 18545911.
17. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427-9. PMID: 18385495.
18. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008 May;28(5):484-95. PMID: 18294250.
19. Schroeder BM. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. Am Fam Physician. 2003 Mar 15;67(6):1392, 5-7. PMID: 12674472.
20. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. 2000 2000 Nov 15;62(10):2359-60. PMID: 11126860.

21. Hazard E, Munakata J, Bigal ME, et al. The burden of migraine in the United States: current and emerging perspectives on disease management and economic analysis. Value in Health. 2009 Jan;12(1):55-64. PMID: 18671771.
22. Lainez MJ, Freitag FG, Pfeil J, et al. Time course of adverse events most commonly associated with topiramate for migraine prevention. Eur J Neurol. 2007 Aug;14(8):900-6. PMID: 17662012.
23. Luykx J, Mason M, Ferrari MD, et al. Are migraineurs at increased risk of adverse drug responses? A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine. Clin Pharmacol Ther. 2009 Mar;85(3):283-8. PMID: 18987621.
24. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID: 16686915.
25. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63(12):2215-24. PMID: 15623677.
26. Gunner KB, Smith HD, Ferguson LE. Practice guideline for diagnosis and management of migraine headaches in children and adolescents: Part two. J Pediatr Health Care. 2008 Jan-Feb;22(1):52-9. PMID: 18174091.
27. Geraud G, Lanteri-Minet M, Lucas C, et al. French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther. 2004 Aug;26(8):1305-18. PMID: 15476911.
28. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. PMID: 19708964.
29. Dowson AJ, Lipscombe S, Sender J, et al. New guidelines for the management of migraine in primary care. Curr Med Res Opin. 2002;18(7):414-39. PMID: 12487508.
30. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9. PMID: 17261680.
31. Solomon S. New appendix criteria open for a broader concept of chronic migraine (Comment on: Cephalagia 2006 Jun:26(6):742-6). Cephalalgia. 2007 May;27(5):469; author reply -70. PMID: 17448186.
32. U.S. Food and Drug Administration. FDA News Release: FDA Approves Botox to Treat Chronic Migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.
33. Pascual J, El Berdei Y, Gomez-Sanchez JC. How many migraine patients need prolonged (>1 year) preventive treatment? Experience with topiramate. J Headache Pain. 2007 Apr;8(2):90-3. PMID: 17221343.
34. Amanzio M, Corazzini LL, Vase L, et al. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain. 2009 Dec;146(3):261-9. PMID: 19781854.
35. Whyte CA, Tepper SJ. Adverse effects of medications commonly used in the treatment of migraine. Expert Rev Neurother. 2009 Sep;9(9):1379-91. PMID: 19769452.
36. Whitlock EP, Lopez SA, Chang S, et al. AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):491-501. PMID: 19540721.
37. Slutsky J, Atkins D, Chang S, et al. Comparing medical interventions: AHRQ and the Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. 2011/03/25 ed. Vol. March 2011. Rockville, MD: Agency for Healthcare Research and Quality; 2008:1-4. Available at www.effectivehealthcare.ahrq.gov.
38. Helfand M, Balshem H. Principles in Developing and Applying Guidance. 2008PMID: 21433405.
39. Higgins J, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration; 2011.
40. Norris S, Atkins D, Bruening W, et al. Chapter 4. Selecting observational studies for comparing medical interventions. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:56-68. Available at: www.effectivehealthcare.ahrq.gov.
41. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2008 Sep 25;63(5):502-12. PMID: 18823754.
42. Rothner AD. Complicated migraine and migraine variants. Curr Pain Headache Rep. 2002 Jun;6(3):233-9. PMID: 12003695.

43. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160. PMID: 14979299.
44. Hansen JM, Thomsen LL, Olesen J, et al. Calcitonin gene-related peptide does not cause the familial hemiplegic migraine phenotype. Neurology. 2008 Sep 9;71(11):841-7. PMID: 18779512.
45. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217.
46. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.
47. Guyatt G, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol. 2011 Aug 10PMID: 21839614.
48. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID: 21784880.
49. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions--agency for healthcare research and quality and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.
50. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Sudbury, MA: Jones and Bartlett; 2003.
51. van der Velde G, van Tulder M, Cote P, et al. The sensitivity of review results to methods used to appraise and incorporate trial quality into data synthesis. Spine (Phila Pa 1976). 2007 Apr 1;32(7):796-806. PMID: 17414916.
52. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006 Dec;59(12):1249-56. PMID: 17098567.
53. Ad Hoc Committee on Classification of Headache. Classification of headache. JAMA. 1962;179(9):717-8.
54. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol. 2009;9:80. PMID: 19961608.
55. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001.
56. Fu R, Gartlehner G, Grant M, et al. Chapter 9. Conducting quantitative synthesis when comparing medical interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:104-19. Available at: http://effectivehealthcare.ahrq.gov.
57. Rucker G, Schwarzer G, Carpenter J, et al. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. Stat Med. 2009 Feb 28;28(5):721-38. PMID: 19072749.
58. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53-77. PMID: 16596572.
59. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351-75. PMID: 15116347.
60. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med. 2010 Dec 20;29(29):3046-67. PMID: 20827667.
61. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. Stat Med. 2007 Jan 15;26(1):37-52. PMID: 16463355.
62. Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. Biom J. 2006 Apr;48(2):271-85. PMID: 16708778.
63. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.
64. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. Eval Health Prof. 2001 Jun;24(2):152-64. PMID: 11523384.
65. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998 Nov 7;317(7168):1309-12. PMID: 9804726.

66. Carlin BP, Louis TA. Bayesian Methods for Data Analysis. Boca Raton, Fla.: Chapman & Hall/CRC; 2009.
67. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID: 16014203.
68. Barden J, Derry S, McQuay HJ, et al. Bias from industry trial funding? A framework, a suggested approach, and a negative result. Pain. 2006 Apr;121(3):207-18. PMID: 16495012.
69. Fox AW. Disease modification in migraine: study design and sample size implications. Headache. 2008 Sep;48(8):1169-75. PMID: 18819175.
70. Arends LR, Hoes AW, Lubsen J, et al. Baseline risk as predictor of treatment benefit: three clinical = meta-re-analyses. Stat Med. 2000;19:3497-518.
71. Russell MB, Hilden J, Sorensen SA, et al. Familial occurrence of migraine without aura and migraine with aura. Neurology. 1993 Jul;43(7):1369-73. PMID: 8392151.
72. Gentile G, Missori S, Borro M, et al. Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine. Journal of Headache & Pain. 2010 Apr;11(2):151-6. PMID: 20213484.
73. Schurks M, Zee RY, Buring JE, et al. ACE D/I polymorphism, migraine, and cardiovascular disease in women. Neurology. 2009 Feb 17;72(7):650-6. PMID: 19221299.
74. Feldman HL. Pushing drugs: genomics and genetics, the pharmaceutical industry, and the law of negligence. Washburn Law Journal. 2003;42(3):575-99. PMID: 15115000.
75. Aurora SK, Gawel M, Brandes JL, et al. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache. 2007 Apr;47(4):486-99. PMID: 17445098.
76. Lampl C, Huber G, Adl J, et al. Two different doses of amitriptyline ER in the prophylaxis of migraine: long-term results and predictive factors. Eur J Neurol. 2009 Aug;16(8):943-8. PMID: 19456855.
77. Mathew NT, Frishberg BM, Gawel M, et al. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Apr;45(4):293-307. PMID: 15836565.
78. Bingham MF, Johnson FR, Miller D. Modeling choice behavior for new pharmaceutical products. Value in Health. 2001 Jan-Feb;4(1):32-44. PMID: 11704970.
79. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006 May 8;166(9):1021-6. PMID: 16682577.
80. Edwards IR. Off-label pharmacovigilance. Drug Safety. 2011 Oct 1;34(10):795-7. PMID: 21879775.
81. Layton D, Hazell L, Shakir SA. Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management. Drug Safety. 2011 Dec 1;34(12):e1-9. PMID: 22077508.
82. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol. 1997 Sep;54(9):1141-5. PMID: 9311358.

Introduction

Migraine is a central nervous system disorder characterized by vascular headaches.[1] Migraine headaches range from moderate to very severe, can cause debilitating pain, and last from 4 to 72 hours.[2 3] In the United States, migraine affects 17 percent of women and 6 percent of men.[4-7] The cumulative lifetime incidence of migraine in the U.S. population is 43 percent for women and 18 percent for men.[8]

Although the frequency and severity of migraine vary considerably, prevention should be considered for episodic migraine defined as ≥4 monthly migraine days with normal functioning or ≥2 migraine days with severe impairment.[9] For 8 to 13 percent of those who experience migraine, the condition is chronic[10] (defined by the National Headache Foundation as migraine that occurs >15 days per month for at least 3 months).[11, 12] Chronic migraine significantly affects patients' physical, psychological, and social well-being and can impose serious lifestyle restrictions.

Migraine also exacts a heavy economic toll. Each year, lost work time and diminished productivity from migraines cost American employers $225.8 billion.[13-15] Forty percent of those affected might benefit from preventive medication,[5, 16, 17] thus reducing lost productivity and work time. Yet, results from several studies demonstrate that only 12.4 percent of adults who experience migraine take preventive medication.[4, 5, 16, 17]

Migraine pain results primarily from increased activity of several agents that regulate blood vessels and sensory function of the brain.[1] In about 15 percent of patients, migraine attacks may be accompanied by aura (visual, sensory, or language symptoms). Other accompanying symptoms may include photophobia (excessive sensitivity to light), phonophobia (fear of loud sounds), osmophobia (hypersensitivity to smells), nausea, or vomiting.[2]

Preventive medications from several drug classes presumably affect various aspects of migraine pathophysiology.[18, 19] The four drugs approved by the U.S. Food and Drug Administration (FDA) for episodic migraine prevention in adults are propranolol, timolol, topiramate, and divalproex sodium.[20] For chronic migraine, the FDA has approved only one drug, botulinum toxin. Doctors also prescribe off-label drugs (approved for clinical conditions other than migraine prevention) for migraine prevention, which include novel antiepileptic drugs, calcium channel modulators, glutamate blockers, and several other drug classes.[20, 21]

Preventive treatment aims to eliminate headache pain.[22-24] However, some degree of pain often persists; therefore, treatment success is usually defined by a decrease in migraine frequency by ≥50 percent after 3 months.[2] In addition to pain relief, preventive drugs can also decrease severity of migraine attacks, use of acute drugs, improve quality of life, normalize brain activity, and eliminate photophobia, phonophobia, nausea, and vomiting.[25, 26]

Long-term adherence to preventive treatments is low. Between 17 and 29 percent of patients discontinue medication because of adverse effects such as anxiety, nausea, vomiting, reduced sleep time, drowsiness, and weakness.[27, 28] Drug choices are based on efficacy and adverse effects as well as headache frequency, presence of aura, and comorbid conditions.[11, 22, 23, 29-33] Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month,[1] while others suggest it for those who experience a headache on most days of the month.[11, 12, 34] Often, preventive treatment is recommended for only 6 to 9 months; however, very limited research exists regarding migraine frequency after discontinuation of preventive treatment.[2]

Several gaps remain in published literature on preventive treatments for migraines. Systematic reviews have focused on the efficacy of specific drugs rather than comparative effectiveness of all available options for pharmacological and nonpharmacological treatment.[35] Little attention has been paid to the comparative effectiveness of off-label drugs used for migraine prevention. Published reviews have not examined quality of life. Clinical reviews have compared the safety with only a few drugs.[35, 36] Patients with chronic migraine comprise the majority of those seen in headache specialty clinics that practice multidisciplinary coordinated care.[8]

Our review focuses on the comparative effectiveness and safety of the drugs used for migraine prevention in adults; our results may help inform treatment recommendations. By the nature of the question, the review focuses on outpatient care.

After discussion with key informants[37] we formulated a list of eligible pharmacological classes. We conducted a comprehensive literature review following the principles in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program[38, 39] and PRISMA guidelines[40] (CRD42012001918).[41]

Key Questions

Question 1

What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults?

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 2

What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 3

Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?

Methods

Search Strategy

We searched for published studies in several databases including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database to find original studies published in English up to March 29, 2012. We searched the FDA website for medical and statistical reviews of the eligible drugs. We searched clinical trial registries including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry to find ongoing, completed, and published trials of migraine prevention. The Scientific Resource Center requested Scientific Information Packets from appropriate manufacturers (Appendix A) per usual procedures. We did not contact the investigators of the primary studies for missing data or clarifications.

To identify related articles, we developed an *a priori* search strategy based on relevant medical subject heading (MeSH®) terms, text words, and weighted word-frequency algorithms. Exact search strategies are shown in Appendix A.

Searches for relevant literature involved several steps: (1) evaluating previously published systematic reviews,[42] (2) conducting a comprehensive literature search in the databases listed above to retrieve identified references, (3) screening abstracts against the inclusion/exclusion criteria, and (4) reviewing full text articles of eligible studies to determine potential inclusion in the synthesis.

Eligibility

We followed the AHRQ *Methods Guide* to select evidence from controlled trials and observational studies.[43] Three investigators independently determined study eligibility according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.[44] We used all included randomized controlled trials (RCTs) to assess effectiveness with drugs. We used all included RCTs and nonrandomized studies to assess adverse effects and treatment discontinuation due to adverse effects.[43] To assess harms of treatments, we included published and unpublished evidence of the adverse effects of drugs in patients with migraine.[45] We defined harms as a totality of all possible adverse consequences of an intervention[45] and analyzed all harms, regardless of how authors perceived causality of treatments.

We defined eligible preventive treatments, outcomes, time, and outpatient setting following the analytical PICOTS framework (Figure 1 and Appendix B). We formulated a list of eligible interventions following discussions with key informants and technical experts and after consideration of public comments (Table 1 Appendix B).

Inclusion Criteria

1. Original epidemiologic studies that aimed to examine preventive pharmacological treatments for migraine.
2. Publication in English.
3. Target population of community-dwelling adults with episodic migraine, chronic daily headache, or chronic migraine defined according to International Headache Society criteria for chronic migraine.[11]
4. Eligible intermediate and patient-centered outcomes as listed in Figure 1.

5. Drugs approved by the FDA for migraine prevention and off-label drugs examined in clinical trials.

We reviewed RCTs that included adults with migraine, comorbid headache disorders, or tension headache if they examined prevention of migraine.

Exclusion Criteria

1. Studies of treatments aimed at acute migraine attacks.
2. Studies that involved patients with migraine variants, such as hemiplegic migraines, basilar migraine, retinal migraine, complicated migraines, and ophthalmoplegic migraine; hospitalized patients; or patients in emergency rooms.[46, 47 48] Studies of short-term prevention of migraine, including menstrual migraines.
3. Studies that included some patients with migraine but did not separately report those outcomes.
4. Studies that involved surgical treatments for migraine.
5. Preclinical pharmacokinetic studies of eligible drugs; studies that examined the pathophysiology of migraine reporting instrumental measurements or biochemical outcomes.
6. Studies that examined eligible drugs on populations with other diseases.

To assess harms of treatments, we included published and unpublished evidence of the adverse effects of drugs in patients with migraine.[45] We defined harms as a totality of all possible adverse consequences of an intervention[45] and analyzed all harms, regardless of how authors perceived causality of treatments.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.[44] First, we classified studies by their design as either interventional (randomized controlled trials [RCTs], nonrandomized controlled clinical trials, and nonrandomized uncontrolled clinical trials) or observational (cohort or case-control studies, cross-sectional studies, or case series).

Then, using the criteria from the Cochrane tool for bias in interventional studies,[49] we evaluated: (1) random allocation of the subjects to the treatment groups; (2) masking of the treatment status; (3) adequacy of allocation concealment; (4) adequacy of randomization as similarity of the subjects in treatment groups by demographics, migraine frequency and severity, and response to previous treatments; (5) intention-to-treat principles; and (6) selective outcome reporting when compared to methods section in the articles. We assumed a low risk of bias when RCTs met all the risk of bias criteria, a moderate risk of bias if at least one of the risk of bias criteria was not met, and a high risk of bias if two or more risk of bias criteria were not met.[50] We concluded an unknown risk of bias for the studies with poorly reported risk of bias criteria. We assessed risk of bias in nonrandomized studies according to selection and attrition bias.[51]

We evaluated disclosure of conflict of interest by the authors of individual studies and funding sources, but we did not use this information to downgrade quality of individual studies.

Grading the Evidence for Each Key Question

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome and for treatment discontinuation due to harms.[52] We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95 percent confidence intervals (CIs), and pooled sample size was greater than 400.[53] We did not include justification of the sample size into grading of the evidence nor did we conduct *post hoc* statistical power analysis. When appropriate, dose-response association, strength of association, and reporting bias were also included. We evaluated the strength of the association, defining *a priori* a large effect when relative risk was >2 and a very large effect when relative risk was >5.[44] We defined low magnitude of the effect when relative risk is significant but <2. We defined reporting bias as publication bias, selective outcomes reporting, and multiple publication bias. We did not perform formal statistical tests quantifying the biases.[54]

We defined high level of evidence on the basis of consistent findings from well-designed RCTs (Table 1). We downgraded strength of evidence to moderate if at least one of the four strength-of-evidence criteria was not met; for example, the studies had moderate risk of bias or the results were not consistent or precise. We downgraded strength of evidence to low if two or more criteria were not met. We defined evidence as insufficient when a single study with high risk of bias examined treatment effects or associations. We applied this approach irrespective of statistical significance of the results.

Table 1. Strength of evidence ranks and definitions

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

Assessing Applicability

We estimated applicability of the population by evaluating the selection of adults with migraine in observational studies and clinical trials.[55] Studies of community-dwelling adults receiving drug treatments with 6 months followup or more had high applicability, as did large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases.

Data Extraction

Researchers used standardized forms to extract data (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041370_1-t_yAjBY2Cn). We conducted a double independent quality control for the data extracted from RCTs; one reviewer abstracted an article and a second reviewed the abstracted data for accuracy. We assessed errors by comparing established ranges for each variable with data charts from the original articles and discussed detected discrepancies. We abstracted the information relevant to the PICOTS framework. We abstracted minimum datasets to reproduce the results presented by the authors. For categorical variables we abstracted the number of events among treatment groups to calculate rates, relative

risk, and absolute risk differences. Means and standard deviations of continuous variables were abstracted to calculate mean differences with a 95 percent CI.

For RCTs in the quantitative analysis set, we abstracted the number randomized to each treatment group as the denominator and calculated estimates by applying intention-to-treat principles. We abstracted the time when the outcomes were assessed as weeks from randomization and the time of followup after treatments.

We abstracted inclusion and exclusion criteria, drug regimen and doses, and patient characteristics (demographics, migraine definition, baseline frequency, severity, and prior treatment status) as factors that can modify treatment effects. We abstracted sponsorship of the studies, sponsor participation in study design and in analysis and presentation of data, and conflict of interest by the authors.

Data Synthesis

We summarized the results into evidence tables. We focused on patient-centered outcomes, such as ≥50 percent reduction in migraine attacks from baseline, quality of life, patient satisfaction, and composite measures of response, including frequency and severity of migraine. We incorporated risk of bias in individual studies into the synthesis of evidence by using individual risk of bias criteria rather than a global score or a ranking category of overall risk of bias.[56, 57] Synthesis of evidence about comparative benefits and safety with drugs from individual RCTs was restricted to studies with low or moderate risk of bias.[22]

We synthesized the evidence according to patient characteristics that could modify treatment effect, including age, sex, race, and duration of migraine, baseline frequency and severity of acute migraine attacks, presence of aura, previous drug treatments, history of drug overuse, and others described in the PICOTS framework. We addressed the role of comorbidities and concomitant treatments in association with patient-centered outcomes. When possible, based on the reporting in original studies, we conducted subgroup and sensitivity analyses according to patient characteristics, drug dose, and timing of followup.

We examined whether the definition of migraine could contribute to the differences in trial results. The FDA approved four drugs for prevention of episodic migraine based on trials conducted before the implementation of the recent migraine definition proposed by the International Headache Society.[11] Thus, eligible studies published before 2004 defined classic or common migraine according to the Ad Hoc Committee on Classification of Headache.[58]

Using Meta-Analyst[59] and STATA®[60] software at a 95 percent CI, we calculated the relative risk and absolute risk difference from the abstracted events, and the mean differences in continuous variables from the reported means and standard deviations. We used a logarithmic scale to analyze the adjusted regression coefficient with a standard error of association between treatments and patient-centered outcomes. We used correction coefficients and intention to treat as recommended calculations for missing data.[44] We synthesized sparse data defined as rates less than 2 percent by calculating fixed Mantel–Haenszel relative risk and Peto odds ratio.[61] When studies had no events with active, control, or both treatments, we used correction coefficients and calculated double arcsine transformation for comparing two proportions and odds ratios from random-effects generalized nonlinear mixed-effect models.[59, 62-65]

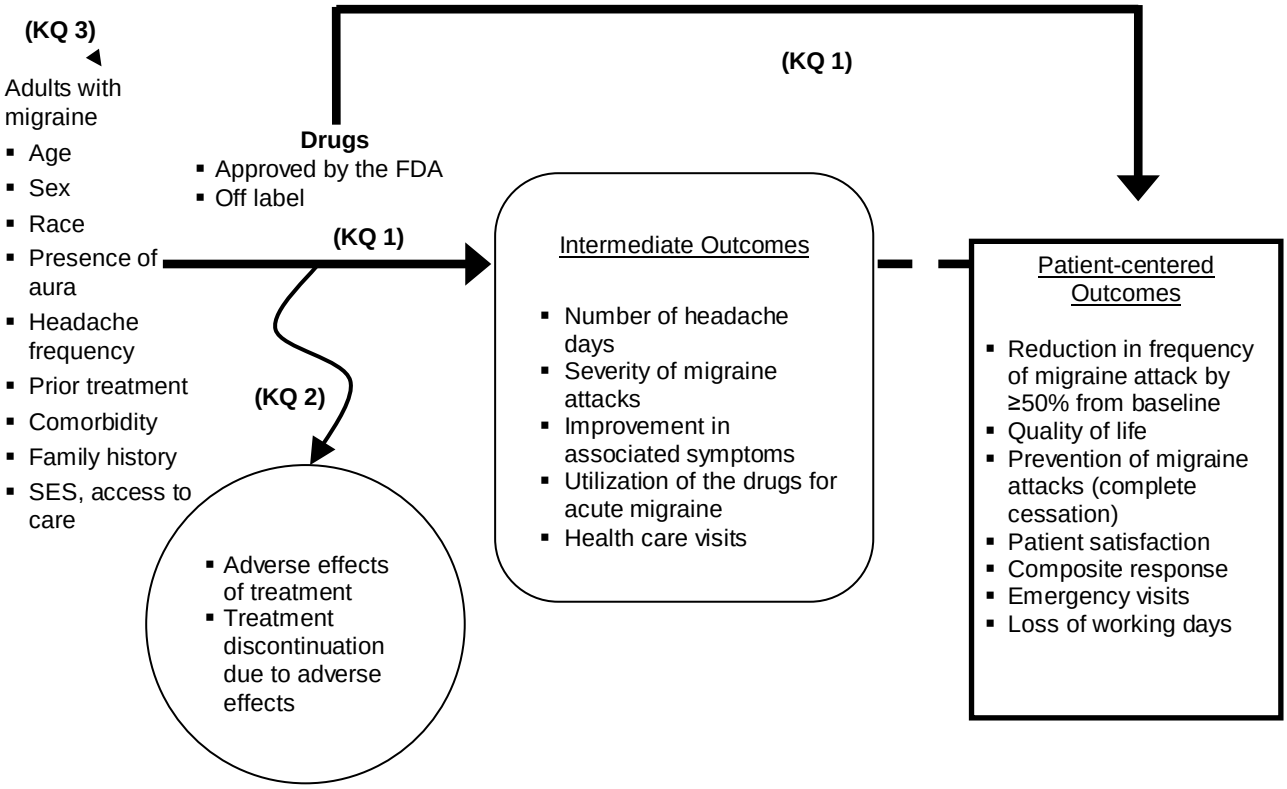
Pooling criteria for Key Questions 1 and 2 included the same active drug treatments and comparators and the same definitions of the outcomes. Standardized mean differences were calculated for different continuous measures of the same outcome.

We tested consistency in the results by comparing the direction and strength of the association[52] and assessed heterogeneity in results with Chi-square and I-square tests.[66, 67] We explored heterogeneity with meta-regression and sensitivity analysis and report the results from random effects models only.[68] We used the random effects model to incorporate in the pooled analysis any differences across trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[61] We explored heterogeneity by risk of bias criteria, disclosed conflicts of interest, study sponsorship, dose and duration of drug treatments, time of followup, inclusion of minorities, proportion of women and elderly adults, and other patient characteristics described above. To avoid ecological fallacy, we did not use patient level variables (for example, mean age or body mass index) in meta-regression.[68]

The number needed to treat to achieve one event of a patient-centered outcome was calculated as reciprocal to absolute risk differences (ARD) in rates of outcome events in the active and control groups.[60, 69] We calculated means and 95 percent CIs for the number needed to treat as reciprocal to pooled ARD when ARD was significant.[70] The number of avoided or excess events (respectively) per population of 1,000 is the difference between the two event rates multiplied by 1,000. We calculated Bayesian odds ratios[59, 65] with 95 percent credible intervals.

For indirect comparisons we conducted Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments.[71] We also used adjusted indirect frequentist comparisons.[72] We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class did not demonstrate significant differences in outcomes. All calculations were performed at 95 percent confidence level.

Figure 1. Framework[73-75]



Abbreviations: KQ = key question; SES = socioeconomic status

Results

We identified 5,089 references and included 308 references (Figure 2). All excluded references are presented in Appendix C. We identified 84 registered studies, 14 of which were published (16 percent). Abstracted data is available in Appendix D with evidence tables (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy). Randomized trials examined 60 drugs from 16 pharmacological drug classes (Appendix Table D1).

Most trials were funded by industry but did not disclose conflict of interest by study investigators (Appendix Table D2). Proportions of industry sponsorship and disclosed conflict of interest varied among drugs (Appendix Table D3). More than half of the RCTs had moderate risk of bias and about a third had low risk of bias (Appendix Table D3). Proportions of RCTs with low risk of bias varied among drugs (Appendix Table D3).

Applicability of study populations was good. Most RCTs were conducted in the United States and Western countries. Published RCTs rarely presented subject flows and did not report why some eligible subjects were not randomized and therefore excluded from the trials (Appendix Table D4). Proportions of eligible subjects excluded from randomization varied among trials. Investigators excluded an average of 5 percent of randomized subjects from the analyses, with substantial variability among the drugs (Appendix Table D4). Investigators recruited patients in clinics in 47 percent of trials, did not report this information in half of RCTs, and clearly indicated community-based recruitment in 3 percent of RCTs. We estimated that investigators had to screen about two patients to enroll one subject in RCTs of antiepileptic drugs or angiotensin II antagonists, three patients to enroll one subject in RCTs that examined beta blockers, and four patients to enroll one subject in RCTs of antidepressants (Appendix Table D4).

More than half of RCTs defined migraine according to the International Headache Society's definition (Appendix Table D5). Older publications used the definition of migraine developed by the Ad Hoc Committee on Classification of Headache, and about 18 percent of RCTs did not specify a migraine definition. Most trials included patients with and without aura. Substantial variability in reporting comorbidities prevented us from using this information in quantitative synthesis of evidence. Most trials, however, excluded patients with severe medical comorbidities or psychiatric illnesses, stroke, and vascular migraine. RCTs rarely reported important patient characteristics that could modify drug effects, including family history of migraine, socioeconomic status, or response to prior preventive treatments (Appendix Table D6). Studies enrolled mostly adults (average age was 35 to 40 years old) and adolescents (Appendix Table D7). Women comprised a majority of the enrolled subjects (Appendix Table D8).

Few trials reported a proportion of obese subjects, but many participants were overweight according to the average body mass index (25.8kg/m2). Enrolled patients had an average of six migraine attacks/month (Appendix Table D9). Loss of followup averaged around 13 percent and was highest with off-label antidepressants (Appendix Table D10). Patient age and baseline migraine frequency were similar in most trials (Appendix Table D11).

Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults?

Studies examined four approved drugs for episodic migraine (topiramate, divalproex, propranolol, and timolol), one approved drug for chronic migraine (botulinum toxin), and 55 off-

label preventive drugs. Clinically important reduction in episodic migraine frequency by ≥50 percent was examined with 41 different drugs from 13 drug classes, including four approved and 37 off-label drugs. Most trials examined a monotherapy with one active agent compared to placebo or another drug. Treatments lasted an average of 19 weeks (from four to 68 weeks). RCTs rarely reported exact drugs and doses of concomitant treatments. However, most trials disallowed concomitant drugs during the run-in period and after randomization, thus implying no concomitant treatments in the RCTs. Strength of evidence was low due to moderate or high risk of bias and imprecise estimates from individual or meta-analyzed RCTs (Table A).

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?

All approved drugs, off-label beta blockers, and angiotensin inhibiting drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent in individual patients (clinical response). When we analyzed how many patients experienced this level of clinical response we found that only one off-label drug, captopril, resulted in more than 500 attributable to active drugs cases per 1,000 treated. Other drugs achieved 200 to 400 cases of clinical response per 1,000 treated. Only a few RCTs examined quality of life, providing no consistent evidence of improvement with examined drugs.

Prevention of Chronic Migraine

Muscle Relaxants

Botulinum Toxin

We identified 15 RCTs of 4,566 adults that examined efficacy of botulinum toxin for migraine prevention (Evidence Table D12). The studies enrolled an average of 285±253 patients aged 18 to 65 years with four to 12 migraine attacks/month. Most trials included patients with 10 or more years of migraine experience. Women comprised 85 percent of participants. More than half of enrolled patients had been previously treated with preventive medications for migraine. Most RCTs were industry funded and reported conflict of interest by study investigators (Evidence Table D13). All RCTs were double blind and most had low risk of bias (Evidence Table D14).

Botulinum toxin was better than placebo in reducing monthly migraine attacks by ≥50 percent (three RCTs of 459 adults, low strength of evidence) (Table 2 and Appendix Table D15).[76-78] Botulinum toxin tended to increase the likelihood of ≥50 percent reduction in migraine frequency compared to placebo in all RCTs (Appendix Table D15). Pooled relative increase by 50 percent achieved statistical significance (pooled RR 1.5, 95 percent CI, 1.2 to 1.8). Pooled analyses demonstrated that 170 adults per 1,000 treated (95 percent CI, 82 to 258) would experience ≥50 percent reduction in migraine frequency (Table 2).

For intermediate outcomes, the absolute number of migraine attacks did not differ between botulinum toxin and placebo (Appendix Table D17). Improvement in migraine severity was inconsistent across four RCTs (Appendix Table D18).[76, 79-81] Improvement in migraine disability assessment was inconsistent across two RCTs (Appendix Table D18).[77, 82] A single RCT of patients who had not benefitted from previous oral prophylactic treatment demonstrated significant improvement in most domains of quality of life as assessed by the Migraine Impact

Questionnaire (Appendix Table D18).[82] Significant improvement was demonstrated in global assessment, severity of migraine symptoms, better self-management of migraine, and ability to work and participate in recreational activities (Appendix Table D18).[82]

Tizanidine

Tizanidine was better than placebo in reducing migraine severity (one RCT of 136 adults), but had no effect on migraine frequency.[83]

Prevention of Episodic Migraine

Antiepileptics

Topiramate

Twenty-three RCTs and two pooled analyses of individual patient data from RCTs examined efficacy of topiramate versus placebo for migraine prevention in adults **(**Appendix Table D19). Trials enrolled 10,100 adults with an average sample size of 439±359. Women constituted 90 percent of enrollees. Patients had an average 7±4 migraine attacks/month at baseline. The proportion of patients without aura varied from 65 percent[84] to 100 percent.[85] Most trials were funded by industry (Appendix Table D20). All trials were double blind and most had low risk of bias (Appendix Table D21).

Topiramate in doses of 50, 100, or 200 mg/day was better than placebo in reducing monthly migraine frequency by ≥50 percent (high strength of evidence) (Table3 and Appendix Table D22). The results were consistent across the studies and robust regardless of pooling methods (Appendix Table D23). Topiramate was also better than placebo in reducing monthly migraine days by ≥50 percent (high strength of evidence) (Table 4). Topiramate, 100 mg/day, decreased the absolute number of migraine days by 5 days/month in pooled analyses of RCTs (Appendix Table D24). Topiramate failed to achieve a complete cessation of migraine.

The reduction in migraine severity scores was inconsistent across the studies (Appendix Table D25). Individual RCTs demonstrated significant improvement in quality of life as measured by scores on the Headache Impact Test,[86] Migraine Specific Questionnaire,[87] and Migraine Disability Assessment (MIDAS) (Appendix Table D26).[88] Improvement in disability was large and clinically important in adults with chronic migraine according to the RCT from the TOPMAT-MIG-201 (TOP-CHROME) Study Group (Appendix Table 26).[88] Topiramate was better than placebo in improving general health status in a previously published pooled analysis of individual patient data from RCTs (Appendix Table D28).[89] Medical Outcome Study Short Form 36 (SF-36) scores improved by more than 200 percent for self-reported vitality and more than 100 percent for improvement in pain and general health (Appendix Table D27).[89]

Topiramate was better than placebo in reducing use of acute drugs (Appendix Table D28). Most individual RCTs demonstrated a small but significant reduction in the number of medications taken or in the reduction of days when drugs for acute attacks were needed (Appendix Table D28).

Divalproex (Table 5)

Three RCTs of 590 adults examined the efficacy of divalproex for migraine prevention in adults. The average sample size was 174±66, and the average age of enrollees was 42±3 years. Women constituted 82 percent of all enrollees (Appendix Table D29). Patients had an average of

six migraine attacks/month at baseline. All three RCTs were funded by industry (Appendix Table D30) and all were double blind (Appendix Table D31).

Divalproex was better than placebo in reducing monthly migraine frequency by ≥50 percent (two RCTs of 346 patients, low strength of evidence) (Appendix Table D32).[90, 91] A larger dose of divalproex (1500 mg/day) was effective in reducing by ≥50 percent migraine-related effects, including impairment of usual activities, need for symptomatic medication, and nausea, vomiting, phonophobia, or photophobia (Appendix Table D33).[92] Evidence was low due to imprecise treatment effect.[92] We estimated that 200 to 300 patients per 1,000 treated would experience clinically important reduction in migraine attacks attributable to divalproex (Table 5).

Valproate

Two small RCTs of 75 adults examined efficacy of valproate for migraine prevention in adults (Table 6 and Appendix Table D29). Trials enrolled adults with a mean age of 40±9 years. Women constituted 82 percent of enrollees. Patients had an average of six migraine attacks/month at baseline. Both trials were double blind and had moderate risk of bias because investigators did not use planned intention-to-treat principles (Appendix Table D31).

Valproate in a dose of 1,000 to 1,500 mg/day was better than placebo in reducing monthly migraine frequency by ≥50 percent (one RCT of 43 patients, low strength of evidence (Table 6).[93] We estimated that 256 patients per 1,000 treated (95 percent CI, 77 to 435) would experience clinically important reduction in migraine attacks attributable to valproate.[93] Valproate decreased the frequency of migraine attacks and severe attacks,[94] duration of attacks,[94]and the use of drugs for acute attacks[93] (Appendix Table D34).

Beta Blockers

Propranolol

Nineteen publications of 18 RCTs examined the efficacy of propranolol versus placebo for migraine prevention in adults (Table 7 and Appendix Table D35). Trials enrolled 1,501 adults with an average sample size of 80±124. Women constituted 76 percent of enrollees. Patients had an average of five migraine attacks/month at baseline. Most trials failed to report funding sources (Appendix Table D36). All trials were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D37).

Propranolol was better than placebo in reducing migraine monthly frequency by ≥50 percent (five RCTs of 560 adults, low strength of evidence due to risk of bias and imprecision) (Appendix Table D38). Preventive effect of propranolol was consistent across the studies (Appendix Table D39). Propranolol caused a small but significant decrease in the absolute number of monthly migraine attacks (mean difference -1, 95 percent CI, -2 to -0.3).[95-98]

A single RCT demonstrated that propranolol decreased analgesics utilization (mean difference -0.3, 95 percent CI, -0.4 to -0.1 doses per patient day) and use of abortive ergotamine for acute attacks (mean difference -0.1, 95 percent CI, -0.3 to -0.1 doses per patient day).[99]

Timolol

Timolol (three RCTs of 276 adults, moderate strength of evidence) (Appendix Table D40) was better than placebo in reducing monthly migraine attacks by ≥50 percent (Appendix Table D41).[97, 100, 101] We estimated that 265 adults per 1,000 treated with timolol (95 percent CI, 154 to 377) would experience a ≥50 percent reduction in monthly migraine attacks (Table 8). Timolol

also decreased an absolute number of migraine attacks and severity of headaches (Appendix Table D42).

Off-label Drugs

Off-label Antiepileptic Drugs

Eight RCTs examined six off-label antiepileptic drugs, including acetazolamide, gabapentin, vigabatrin, oxcarbazepine, carbamazepin, and lamotrigen (Appendix Table D43). Most trials were sponsored by industry (Appendix Table D44) and all were double blind (Appendix Table D45).

Carbamazepin (one RCT of 96 adults, low strength of evidence) and gabapentin (two RCTs of 139 patients, low strength of evidence) were better than placebo in reducing monthly migraine attacks by ≥50percent (Table 9). Individual RCTs found that oxcarbazepine and acetazolamide were not better than placebo in preventing migraine attacks (Table 9).

In addition to off-label antiepileptic drugs examined in RCTs, pregabalin was examined in one open label uncontrolled trial.[102] Pregabalin was associated with a significant decrease from baseline in headache frequency and severity and with global improvement defined as ≥50 in visual analog scale (VAS) score in 40 percent of patients.[102]

Beta Blockers

Seventeen RCTs examined the effects of off-label beta blockers versus placebo for migraine prevention in adults (Table 10 and Appendix Table D46). Most trials failed to report funding and conflict of interest (Appendix Table D47). All trials were double blind with moderate risk of bias because the investigators did not use planned intention-to-treat principles (Appendix Table D48).

Metoprolol

Metoprolol was better than placebo in markedly reducing migraine attacks (moderate strength of evidence from two RCTs of 225 adults) (Appendix Tables D49 and D50).[103, 104] Pooled analysis found a significant increase in the likelihood of a clinical response (Appendix Table D51)[103, 104] but no effect on absolute number of migraine attacks (Appendix Table D52).[103-105]

Metoprolol reduced severity of migraine attacks in a single RCT (Appendix Table D51).[104] Regarding use of drugs for acute attacks, evidence with metoprolol was mixed; one trial reported reduced use of such drugs and a second reported increased analgesic use (Appendix Table D52).[103, 104]

Atenolol

Atenolol (one RCT of 48 adults, low strength of evidence) (Appendix Table D50) was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 10).[106] Atenolol significantly reduced use of ergotamine drugs in a single RCT (Appendix Table D47).[106]

Nadolol

Nadolol (one RCT of 32 adults, low strength of evidence) (Appendix Table D50) was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 10).[107] In a single RCT, nadolol improved perceived relief in frequency, intensity, and severity of migraine attacks (Appendix Table D47).[107]

Alprenolol

Alprenolol (one RCT of 33 adults, low strength of evidence) (Appendix Table D50) was not better than placebo in achieving perceived treatment success (Table 10).[108] Alprenolol did not reduce the absolute number of monthly migraine attacks or Headache Index scores (Appendix Table D49).[108]

Pindolol

Pindolol (one RCT of 28 adults) was not better than placebo in reducing monthly migraine attacks by ≥50 percent (Appendix Table D48).[109] Pindolol did not reduce the absolute number of monthly migraine attacks or Headache Index scores (Appendix Table D49).[109]

Antidepressants

Twenty-four RCTs examined the effectiveness of off-label antidepressants for migraine prevention in adults (Appendix Table D53). Trials enrolled 2,687 adolescents and adults with episodic migraine. Most trials that reported funding were sponsored by industry (Appendix Table D54). Most trials were double blind with moderate risk of bias (Appendix Table D55).

Amitriptyline

Amitriptyline (two RCTs of 228 adults, low strength of evidence) (Table 11) was better than placebo in reducing monthly migraine attacks by ≥50 percent.[110]

Fluoxetine

Fluoxetine (one RCT of 32 adults, low strength of evidence) (Table 11) was not better than placebo in achieving an excellent self-reported clinical response.[111]

Tonabersat

Tonabersat (one RCT of 124 adults, low strength of evidence) (Table 11) was better than placebo in reducing monthly migraine attacks by ≥50 percent.[112]

Venlafaxine

Venlafaxine (one RCT of 60 adults, low strength of evidence) (Table 11) in a dose of 150 but not 75 mg/day was better than placebo in achieving an excellent self-reported clinical response.[113]

Calcium Channel Antagonists

Eleven RCTs examined calcium channel blockers for migraine prevention in adults (Appendix Table D56). Most trials were sponsored by industry and failed to disclose conflict of interest (Appendix Table D57). All trials were double blind, with moderate risk of bias (Appendix Table D58).

Nimodipine

Nimodipine was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 12).[114] Rates of complete cessation of migraine were also significantly greater with nimodipine than placebo.[115]

Nicardipine

Nicardipine was better than placebo in reducing migraine intensity and absolute number of migraine attacks.[116]

Verapamil

Verapamil was better than placebo in reducing composite migraine score and achieving patient satisfaction.[117, 118] Verapamil also reduced use of drugs for acute attacks.[117]

Angiotensin Converting Enzyme Inhibitors

Two RCTs examined the effects of ACE inhibitors for migraine prevention in adults (Appendix Table D59).[119 120] One industry-funded RCT examined lisinopril (Appendix Table D60).[119] One RCT that did not report funding source or conflict of interest examined captopril.[120] Both trials were double blind with low risk of bias (Appendix Table D61).

Captoptil

Captoptil (one RCT of 12 adults, low strength of evidence) was examined in a small RCT that enrolled adults with comborbid hypertension and depressive symptoms for whom drugs had previously failed to prevent migraines.[120] Captoptil was better than placebo in achieving complete cessation of migraine and improvement in Headache Index scores by more than 60 percent (Table 13).[120] The effect was large. We estimated that 667 patients per 1,000 treated experienced no migraine (95 percent CI, 388 to 946).[120] Captopril was also better than placebo in reducing depression symptoms.[120]

Lisinopril

Lisinopril (one RCT of 60 adults, low strength of evidence) was better than placebo in reducing migraine days and severity of symptoms (Table 13).[119] Lisinopril also reduced the absolute number of migraine days and body pain measured with SF36, but did not decrease use of drugs for acute attacks.[119]

Angiotensin II Receptor Antagonists

Two RCTs examined the effects of angiotensin II receptor antagonists for migraine prevention in adults (Appendix Table D59).[121, 122] Both trials were funded by industry and reported conflict of interest (Appendix Table D60).[121, 122] Both trials were double blind (Appendix Table D61).

Candesartan

Candesartan (one RCT of 60 adults, low strength of evidence) was better than placebo in achieving ≥50 percent reduction in migraine days, hours, and severity (Table 13). Candesartan also decreased migraine related disability but had no effect on use of drugs for acute attacks.[121]

Telmisartan

Telmisartan (one RCT of 95 adults, low strength of evidence) was not better than placebo in reducing monthly migraine attacks by ≥50 percent (Table13).[122] Telmisartan reduced the absolute number of migraine days but had no effect on use of drugs for acute attacks.[122]

Antiadrenergics

Clonidine

Thirteen RCTs examined clonidine for its effects on migraine prevention in adults (Appendix Table D62). Most trials failed to report funding and conflict of interest (Appendix Table D63). Most trials were double blind but did not use intention-to-treat principles (Appendix Table D64). Only one trial reported clinically important reduction in migraine and found that clonidine was superior to placebo in reducing monthly migraine attacks by ≥50 percent (Table 11).[123] Clonidine was not better than placebo in increasing the number of patients considered better according to self-reported global assessment.[124] Clonidine was better than placebo in reducing migraine duration[125] and use of drugs for acute attacks.[126]

Guanfacine

Guanfacine was better than placebo in reducing monthly migraine days and migraine days with nausea or vomiting in a small low risk of bias RCT.[127]

Ergot Alkaloids

Nine RCTs examined effectiveness of ergot alkaloids for migraine prevention in adults (Appendix Table D65). Trials enrolled 1,040 adolescents and adults with episodic migraine. Trials failed to report funding and conflict of interest (Appendix Table D66). Most trials were double blind with moderate risk of bias (Appendix Table D67).

Dihydroergotamine

Dihydroergotamine (one RCT of 384 adults, low strength of evidence) (Table 14) was not better than placebo in reducing monthly migraine attacks by ≥50 percent.[128]

Leukotriene Receptor Antagonists

Montelukast

Montelukast (one RCT of 177 adults) was not better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 12).[129]

Nonsteroid Anti-inflammatory Drugs

Individual RCTs demonstrated that aspirin, flurbiprofen, and fenoprofen were effective in reducing migraine frequency by ≥50 percent (Table 15).

Antipsychotic Drugs

Published RCTs did not examine antipsychotic drugs for migraine prevention. Quetiapine was examined in one uncontrolled trial of refractory migraine, defined as previous unresponsiveness to the combination of atenolol, nortriptyline, and flunarizine.[130] Adult patients with <15 days of headache per month who were not overusing symptomatic medications were treated with quetiapine (75mg/day) for 10 weeks. Reduction in migraine frequency by ≥50 percent was achieved in 65 percent of the patients.[130] Patients also experienced a significant reduction in migraine days (from 10.2 to 6.2 per month) and use of drugs for acute attacks (from 2.3 to 1.2 days/week).[130]

Antidementia Drugs

Published RCTs did not examine antidementia drugs. Retrospective review of case series and case reports demonstrated that with memantine treatment, 60 percent of the patients experienced ≥50 percent reduction in monthly migraine frequency, and 80 percent experienced a significant reduction in frequency of aura.[131, 132]

b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?

Individual RCTs provided low strength of evidence about comparative effectiveness of drugs, finding few significant differences (Table C in the Executive Summary). Network Bayesian meta-analysis demonstrated that ACE inhibitors, angiotensin II receptor antagonists, propranolol, and off-label beta blockers are more effective than all other drugs (Table D in the Executive Summary).

Approved Drugs

Muscle Relaxants

Botulinum Toxin

Five RCTs of 350 adults examined comparative effectiveness of botulinum toxin versus other drugs for migraine prevention (Appendix Table D68). Trials enrolled an average of 70±18 patients ages 18 to 65 with 12 to 24 migraine days per month. Women constituted 91 percent of all enrolled. Trials were funded by industry[133, 134] or grants,[135] with most investigators disclosing conflict of interest (Appendix Table D69). All but one RCT[135] were double blind, with moderate or high risk of bias due to inadequacy of randomization or unplanned intention-to-treat analyses (Appendix Table D70). The trials often concluded that both active treatments were successful based on statistically significant reduction from baseline in absolute number of migraine days or hours. We focus on differences in outcomes at the end of the treatment with active and control drugs.

Comparative effectiveness of botulinum toxin versus topiramate was examined in two RCTs (low strength of evidence) that found no significant differences in likelihood of migraine prevention or improvement in migraine disability assessment (Appendix Table D71).[133, 136] Physicians assessed treatment responses as marked improvement in migraine frequency more often with topiramate than botulinum toxin (ARD 0.33, 95 percent CI, 0.10 to 0.57) (Appendix Table 71).[133] Absolute scores on the Headache Impact Test were significantly better with topiramate than botulinum toxin.[133] Use of drugs for acute attacks did not differ between the two.[133]

Comparative effectiveness of botulinum toxin versus divalproex sodium was examined in a single RCT (low strength of evidence) found no differences in migraine prevention with two drugs (Appendix Table D72).[82] Neither the absolute number of migraine days nor change scores from baseline in the migraine Disability Assessment Scores and/or Headache Impact Test differed between the drugs.[82]

Comparative effectiveness of botulinum toxin versus amitriptyline was examined in a single RCT that found no differences in migraine prevention with the two drugs (Appendix Table D73).[135] Evidence was insufficient due to a high risk of bias in this individual RCT.[135]

Antiepileptics

Topiramate

Nine RCTs of 872 adults examined comparative effectiveness of topiramate with other drugs for migraine prevention (Appendix Table D74). Trials enrolled an average 97±95 adults aged 35±4 with an average of 9±7/monthly migraines. Women constituted 77 percent of enrollees. Most trials did not report funding source or conflict of interest (Appendix Table D75). All but one trial were double blind with low or moderate risk of bias (Appendix Table D76).

Individual RCTs provided low strength of evidence that topiramate was more effective than amitriptyline in reducing monthly headache days by ≥50 percent (one RCT of 347 adults) (Table 16).[137] Topiramate was more effective than lamotrigine in reducing monthly headache intensity by ≥50 percent (one RCT of 120 adults).[138] Differences were small (less than 20 percent absolute risk difference) but statistically significant (Appendix Table D77). Decrease in headache frequency by ≥50 percent did not differ between topiramate and zonasamide,[139] valproate,[140] levetiracetam,[141] or lamotrigine[138] (Table 16). Topiramate was more effective than propranolol in reducing absolute migraine frequency, duration, and intensity (one RCT of 62 adults).[142]

Valproate

One RCT examined comparative effectiveness of valproate versus cinnarizine[143] (Appendix Tables D78 and D79). The trial enrolled 125 adolescents and adults with a mean age of 34 years; enrollees suffered an average of seven attacks/month.[143] This double-blind trial had low risk of bias (Appendix Table D80). Neither the likelihood of a clinically important reduction in monthly migraine frequency nor the duration and intensity of attacks differed between the drugs (Table 17 and Appendix Table D81).[143]

Beta Blockers

Propranolol

Twenty-nine publications of 25 RCTs examined the comparative effectiveness of propranolol for migraine prevention in adults (Table 7 and Appendix Table D82). Trials enrolled 3,469 adults with an average sample size of 131±224. Women constituted 76 percent of enrollees. Most trials failed to report funding (Appendix Table D83). Most trials were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D84).

Propranolol Versus Topiramate (one RCT of 575 adults, low strength of evidence) (Table 7)

The likelihood of ≥50 percent reduction in monthly migraine frequency did not differ between topiramate and propranolol (Appendix Table D37).[95] Topiramate was more effective than propranolol in reducing absolute migraine frequency, duration, and intensity (one RCT of 62 adults).[142] Use of drugs for acute attacks did not differ between the two drugs.[95]

Propranolol Versus Divalproex (one RCT of 74 adults) (Table 7)

The likelihood of ≥50 percent reduction in monthly migraine frequency and headache days did not differ between propranolol and divalproex.[144] Evidence from a single RCT with high risk of bias was insufficient (Appendix Table D38).

Propranolol Versus Clonidine (one RCT of 46 adults, low strength of evidence) (Table 7)

The likelihood of ≥50 percent reduction in migraine days did not differ between propranolol and clonidine (Appendix Table D38).[145]

Propranolol Versus Cinnarizine (one RCT of 28 adults) (Table 7)

Propranolol was more effective than cinnarizine in achieving complete cessation of migraine attacks (low strength of evidence from a single RCT) (Appendix TableD38).[146] Propranolol combined with cinnarizine was more effective in achieving complete cessation of migraine attacks than drugs alone (low strength of evidence from a single RCT) (Appendix Table D38).[146]

Propranolol Versus Metoprolol (two RCTs of 113 adults) (Table 7)

The likelihood of ≥50 percent reduction of the sum of severity scores or clinically important reduction in migraine days did not differ between propranolol and metoprolol (low strength of evidence) (Appendix Table D38).[147, 148] Differences were not significant in either trial or in pooled analysis (Appendix Table D39).

Propranolol Versus Nadolol (one RCT of 140 adults) (Table 7)

Nadolol, 160 mg/day, was more effective than propranolol in achieving a reduction of ≥50 percent in migraine frequency, duration, and intensity (low strength of evidence) (Appendix Table D38).[149] Differences between lower dose of nadolol (80 mg/day) and propranolol (160 mg/day) were not significant.[146, 149]

Propranolol Versus Timolol (three RCTs of 242 adults) (Table 7)

Propranolol was more effective than timolol in reducing monthly migraine frequency by ≥50 percent (low strength of evidence) (Appendix Table D38).[97, 100] The association was consistent in pooled analysis (Appendix Table D39).

Propranolol Versus Nifedipine (two RCTs of 76 adults)

Propranolol was more effective than nifedipine in reducing monthly migraine frequency by ≥50 percent (low strength of evidence) (Appendix Tables D38 and D39).[148, 150]

Propranolol Versus Amitriptyline (one RCT of 108 adults) (Table 7)

The likelihood of ≥50 percent reduction in monthly migraine attacks did not differ between propranolol and amitriptyline (low strength of evidence) (Appendix Table D38).[151]

Propranolol Versus Nortriptyline (one RCT of 49 adults) (Table 7)

The likelihood of ≥50 percent reduction in monthly migraine attacks did not differ between propranolol and nortriptyline (low strength of evidence) (Appendix Table D38).[152] The likelihood of ≥50 percent reduction in the number of migraine days did not differ between a combined therapy using both drugs and propranolol alone.[152]

Propranolol Versus Femoxetine (one RCT of 29 adults*)* (Table 7)

The likelihood of ≥50 percent reduction in monthly migraine attacks did not differ between propranolol and femoxetine (low strength of evidence) (Appendix Table D38).[153]

Off-label Drugs

Off-label Beta Blockers

Seven RCTs examined comparative effectiveness of off-label beta blockers for migraine prevention in adults (Appendix Table D85). The trials failed to report funding and conflict of interest (Appendix Table D86). All trials were double blind (Appendix Table 87).

Metoprolol Versus Bisoprolol (one RCT of 250 adults, low strength of evidence) (Appendix Table D88).[154]

Neither reduction in monthly migraine attacks by ≥50 percent nor absolute number of migraine days differed between metoprolol and bisoprolol (Table 18)[154] (Appendix Table 89).[154, 155]

Metoprolol Versus Nebivolol (one RCT of 30 adults, low strength of evidence) (Evidence Table 88)[156]

Reduction in monthly migraine attacks by ≥50 percent did not differ between metoprolol and nebivolol (Table 18).[156] Neither migraine-related disability, use of drugs for acute attacks (Appendix Table D90), nor quality of life (Appendix Table D89) differed between metoprolol and nebivolol.[156]

Metoprolol Versus Aspirin (two RCTs of 326 adults, low strength of evidence) (Appendix Table D88).[157, 158]

Metoprolol was more effective than aspirin, 300 mg/day,[157] but less effective than aspirin, 1,500 mg/day (Table 18).[158]

Metoprolol Versus Clonidine (one RCT of 62 adults, low strength of evidence) (Appendix Table D98).

Reduction in monthly migraine attacks by ≥50 percent did not differ between metoprolol and clonidine (Table 18).[159] However, more patients noticed a reduction in migraine days with metoprolol than clonidine (Appendix Table D90).[159]

Antidepressants

Evidence of comparative effectiveness of antidepressants was limited to individual RCTs with moderate or high risk of bias.

Femoxetine Versus Propranolol (one RCT of 24 adults, low strength of evidence).[153]

The likelihood of reducing monthly migraine attacks by ≥50 percent did not differ between the two drugs, nor did the duration or intensity of attacks or use of acute drugs.[153]

Fluoxetine + amitriptyline versus amitriptyline (one RCT of 39 adults, low strength of evidence) resulted in similar migraine frequency and severity.[160]

Fluvoxamine versus amitriptyline (one RCT of 64 adults, low strength of evidence) resulted in similar migraine frequency and severity.[161]

Venlafaxine versus amitriptyline (one RCT of 76 adults, low strength of evidence) resulted in similar migraine frequency and severity.[162]

Venlafaxine Versus Escitalopram (one RCT of 105 adults)

Evidence from a single high risk of bias RCT was insufficient to conclude comparative effectiveness of these two drugs.[163]

Indirect Evidence of Comparative Effectiveness of Preventive Drugs

Network Bayesian meta-analyses demonstrated that ACE inhibitors, angiotensin II antagonists, and off-label beta blockers were the most effective drugs for preventing migraine in adults. Propranolol, timolol, metoprolol, and atenolol resulted in significantly greater odds of migraine prevention than antiepileptics, antidepressants, or other off-label drugs. All other drugs had similar effectiveness. Indirect adjusted frequentist analysis of 17 effective (better than placebo) drugs demonstrated that the angiotensin II receptor blocker candesartan was more effective than topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline.

Clinically important reduction in migraine frequency by ≥50 percent was examined with 41 different drugs from 13 drug classes. To find a model that fits the data, we conducted sensitivity analyses of approved individual drugs versus off-label drug classes and individual beta blockers versus other drug classes. We first analyzed the comparative effectiveness of 11 treatments including placebo, topiramate, valproate, divalproex, propranolol, timolol, ACE inhibitors (captopril or lisinopril), angiotensin II antagonists (candesartan, telmisartan), off-label beta blockers (nadolol, metoprolol, atenolol, bisoprolol, nebivolol, pindolol), off-label antidepressants (amitriptyline, femoxetine, fluoxetine, nortriptyline, tonabersat, venlafaxine), off-label antiepileptics (acetazolamide, carbamazepin, gabapentin, lamotrigine, oxcarbazepine, zonasamide), off-label ergot alkaloids (dihydroergotamine, lisuride, methysergide), and other off-label drugs (clonidine, catapresan, cinnarizine, magnesium, aspirin, nifedipine, nimodipine, montelukast). This analysis clearly demonstrated that all drugs excluding ergot alkaloids were better than placebo preventing migraine. Comparative effectiveness analyses demonstrated that ACE inhibitors or angiotensin II antagonists were the most effective in migraine prevention in adults (Appendix Table D91). Off-label beta blockers were the second best treatment for migraine prevention. However, differences in odds ratios were not statistically significant. All other drugs had similar effectiveness.

Next, we analyzed the comparative effectiveness of nine treatments including propranolol, timolol, metoprolol, all other off-label beta blockers (atenolol, nadolol, pindolol, bisoprolol, or nebivolol), all off-label antidepressants, all approved and off-label antiepileptics, ACE inhibitors, or angiotensin II antagonists, and all other off-label drugs. This analysis clearly demonstrated that ACE inhibitors or angiotensin II antagonists were more effective than all other treatments (Appendix Table D92). Propranolol, timolol, metoprolol, and all other off-label beta blockers resulted in significantly greater odds of migraine prevention than antiepileptics, antidepressants, and other off label drugs.

Finally, we analyzed the comparative effectiveness of 12 treatments including topiramate, divalproex, propranolol, angiotensin inhibiting drugs, calcium channel antagonists, antidepressants, antiepileptics, ergot alkaloids, and NSADs (Appendix Table D93). This analysis also clearly demonstrated that all but ergot alkaloids were better than placebo, and that angiotensin inhibiting drugs were more effective than topiramate, divalproex, propranolol, calcium channel antagonists, antidepressants, antiepileptics, and ergot alkaloids.

Indirect adjusted frequentist analysis of 17 effective (better than placebo) individual drugs demonstrated that the angiotensin II receptor blocker candesartan was more effective than

topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline (Appendix Table D94).

c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?

Beta Blockers

Propranolol Versus Biofeedback (one RCT of 192 adults, low strength of evidence)

The likelihood of ≥25 percent reduction in monthly migraine frequency did not differ between propranolol and biofeedback assisted diaphragmatic breathing and systematic relaxation accompanied by home practice of diaphragmatic breathing and systematic relaxation.[164]

Antidepressants

Amitriptyline Versus Spinal Manipulation Alone (one RCT of 147 adults) (Table 19)[165]

Amitriptyline was more effective than spinal manipulation in reducing Headache Index scores by more than half at the end of treatment, but not at post-treatment followup (Appendix Table 95).[165] Strength of evidence was low due to risk of bias and imprecision (Appendix Table 96).[165]

Evidence from a single high risk of bias RCT was insufficient to conclude comparative effectiveness between amitriptyline and biofeedback.[166]

d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?

Five RCTs compared the effectiveness of drugs combined with nondrug treatments to placebo or pharmacological treatments alone (Appendix Table D97). Most trials were funded by nonprofit grants (Appendix Table D98). One trial had low risk of bias, two had moderate, and two high (Appendix Table D99).

Beta Blockers

Behavioral migraine management and relaxation combined with propranolol (maximum dose 240 mg/day) or nadolol (maximum dose 120 mg/day) was more effective than placebo in reducing monthly migraine frequency by ≥50 percent (Appendix Table D100) but did not differ compared with drugs alone.[167] Evidence of effectiveness and safety was low due to imprecise estimates from a single RCT (Appendix Table D101).[167] We estimated that 387 adults per 1,000 treated experienced a reduction in migraine frequency by ≥50 percent (95 percent CI, 157 to 618) with combined therapy (Table 20).[167]

Propranolol (240 mg/day) or nadolol (120 mg/day) combined with behavioral therapy (orientation plus relaxation training, migraine warning signs and triggers, effectively using migraine medication and reducing impact of migraines, stress management or biofeedback training, and migraine management plan) was more effective than placebo in improving self-efficacy (Appendix Table D102).[168]

Evidence was insufficient from a single high risk of bias RCT that compared the effectiveness of propranolol combined with biofeedback and propranolol alone for migraine prevention in adults.[166]

Antidepressants

Amitriptyline Combined With Spinal Manipulation Versus Amitriptyline Alone or Spinal Manipulation Alone (one RCT of 147 adults) (Table 19)[165]

Spinal manipulation was more effective than combined treatment in reducing Headache Index scores.[165] Combined treatment was not more effective than amitriptyline alone in improving general health status or reducing use of drugs for acute attacks (Appendix Table D103).[165]

Evidence from a single high risk of bias RCT was insufficient to conclude comparative effectiveness between amitriptyline combined with biofeedback and the drug alone.[166]

e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Muscle Relaxants

Botulinum Toxin

Dose response Migraine Prevention With Botulinum Toxin

Higher doses of botulinum toxin resulted in a greater decrease in absolute migraine frequency according to the BoNTA-024-026-036 Study Group.[169] Higher doses of botulinum toxin resulted in less frequent use and overuse of acute pain medications at 1 and 3 months of followup according to the BoNTA-039 Study Group (Appendix Table D104).[170] Patients and investigators found no differences in global assessment of improvement with higher doses of botulinum toxin (Appendix Table D105).[81]

Antiepileptics

Topiramate

Increase in topiramate dose from 50 to 100 mg/day resulted in a higher response rate (≥50 percent reduction in monthly migraine frequency) without additional benefit from increasing the dose to 200 mg/day (Appendix Table D106). Higher topiramate doses (50 to 100 mg) resulted in significant migraine prevention of ≥50 percent in one patient for every six treated (Table 21).

Divalproex

Higher doses of divalproex did not result in a greater likelihood of clinically important migraine frequency reduction (Appendix Table D107) (low strength of evidence from one RCT).[92]

Beta Blockers

Propranolol

Increasing propranolol dose did not result in a greater likelihood of clinically important migraine frequency reduction (low strength of evidence from a single RCT).[171-174]

Off-label Beta Blockers

Individual RCTs examined dose response effects with pindolol,[175] nadolol,[176, 177] and bisoprolol.[178]

Pindolol

Pindolol, 15 mg/day, was more effective than 7.5 mg in reducing migraine days and duration.[175]

Nadolol

Nadolol, 160 to 240 mg/day, was more effective than 80 mg/day in reducing migraine frequency and severity.[176, 177]

Bisoprolol

Bisoprolol, 10 mg/day, was more effective than 5 mg/day in reducing migraine duration but not frequency.[178]

Antidepressants

Amitriptyline

Amitriptyline, 50 mg/day, was not more effective than 25 mg/day in reducing migraine frequency or severity.[179]

Venlafaxine

Venlafaxine, 150 mg/day, resulted in excellent global self-reported efficacy more often than 75 mg/day.[113]

e2. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Six RCTs of 3,825 adults examined effectiveness of drug management for migraine prevention in adults (Appendix Table D108). Most trials were sponsored by nonprofit organizations (Appendix Table D109). Half of trials had low risk of bias, and the other half had moderate risk of bias due to inadequacy of randomization (Appendix Table D110). Four RCTs examined the effectiveness of multidisciplinary migraine management programs and two examined the effectiveness of pharmacist-led drug management (Appendix Table D111).

Multidisciplinary Intervention Versus Standard Care

The community-based multidisciplinary intervention included intake by a neurologist, physical therapist, and a psychologist, with group-supervised exercise therapy sessions, massage therapy sessions, and a group lectures with a dietitian[180] (Appendix Table D111). Adherence did

not differ between the multidisciplinary intervention and standard medical care with the patient's primary physician (Appendix Table D112).[180] The multidisciplinary intervention was more effective in improving quality of life and reducing migraine-related disability (Appendix Table D113).[180] We found no statistically significant changes in medication use or work status.[180]

Migraine Management Program Versus Usual Care

A multidisciplinary migraine management program was administered by a midlevel provider (e.g., nurse practitioner or physician assistant) with expertise in migraine evaluation and management.[181] The program included an educational session in which patients received educational materials that described migraine types and etiologies, pharmacologic treatment, triggers, sleep hygiene, and relaxation techniques.[181] Patients in the control group continued with their current clinician, without access to the migraine management program. Fewer adults had migraine-related disability at 6 months of followup with the migraine management program (Appendix Table D114).[181] We estimated that 196 adults per 1,000 treated (95 percent CI, 125 to 258) had no migraine-related disability with the migraine management intervention,[181] which was also more effective than usual care in improving quality of life and treatment satisfaction (Appendix Table D115).[181]

Cognitive Behavioral Minimal Contact Program Versus Usual Care

The cognitive-behavioral minimal contact program consisted of five sessions that provided information about migraine and progressive muscle relaxation, acute and prophylactic migraine medications, and triggers for medication overuse (e.g., availability of drugs, fear of attack and loss of social functioning, and stress level in private and professional life). Participants also established individualized goals for future drug intake and improving quality of life.[182] The cognitive-behavioral minimal contact program did not decrease migraine frequency or duration of migraine related disability (Appendix Table D116)[182] nor did it improve social activity engagement, pain self-management, migraine-related anxiety, and depression.[182] However, patient satisfaction with treatment was significantly greater with the cognitive-behavioral minimal contact program than with usual care.[182]

Headache School Versus Usual Care

The curriculum of a standardized course of didactic instructions regarding migraine biogenesis and management consisted of classes taught by neurologists and migraine sufferers who previously had undergone intensive classroom training. Headache school classes focused mostly on acute preventive drug treatments.[183] Patients in the control group received routine drug management.[183] Patients who overused drugs for acute attacks attended headache school less often than did patients receiving routine drug management (Appendix Table D117).[183] Attending headache school also reduced migraine disability (Appendix Table D118).[183]

Pharmaceutical Care for Migraine Versus Standard Counseling

Pharmaceutical care intervention was defined as intensified structured counseling between patient and pharmacist and the use of drug databases. German pharmacists worked with patients individually to prioritize problems, define goals, and devise plans to work toward goals.[184] Patients in the control group received standard counseling that included general information about benefits and possible adverse drug effects.[184] Pharmaceutical care resulted in a statistically significant improvement from baseline in mental health and self-efficacy.[185] The likelihood of complete migraine cessation did not differ with active and control interventions (Appendix Table

D119)[184] nor did absolute number of migraine attacks or quality of life differ between the active intervention and the control (Appendix Table D120).[184]

Intensive Pharmaceutical Care Campaign Versus Control Pharmacy

Danish pharmacists and pharmacy assistants provided the intervention according to the manual developed by the Danish College of Pharmacy Practice.[185] The campaign targeted inappropriate use of triptans. Intervention pharmacy staff received information about migraine, detection of inappropriate triptan use and other drug-related problems, and techniques for establishing a private dialogue with patients.[185] The campaign had no statistically significant impact on triptans use (Appendix Table D121).[185]

Figure 2. Study Flow

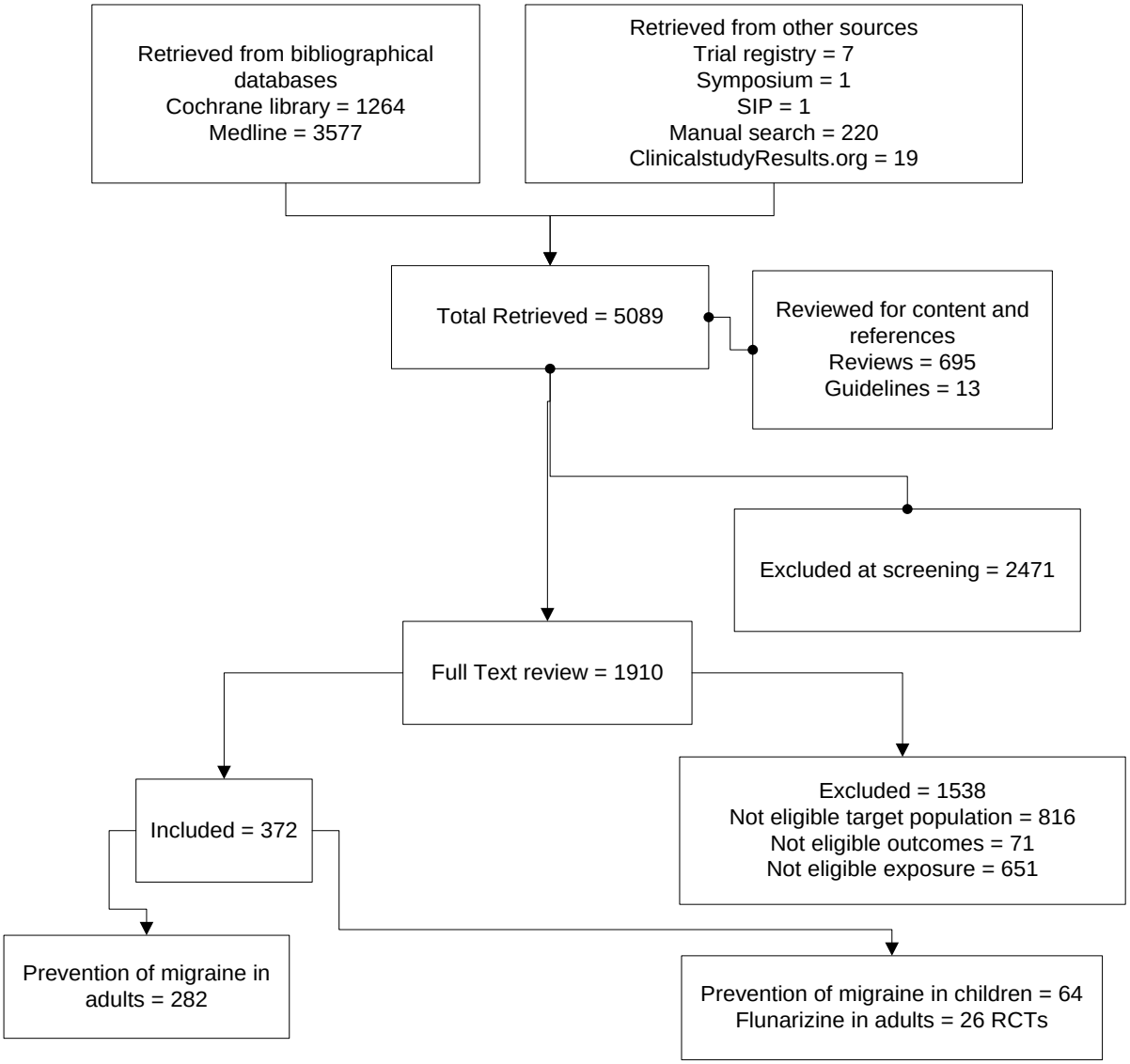


Table 2. Decrease in migraine frequency by ≥50% with botulinum toxin, pooled results from randomized controlled clinical trials, random effects models with inverse variance weights

Sample size, reference	Rate, percent with botulinum toxin [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence	Conclusion
459[76-78]	50.6 [34.4]	6 (4 to 12)	170 (82 to 258)	Low	Botulinum toxin was better than placebo in reducing migraine frequency by ≥50% from baseline

CI – confidence interval

Table 3. Migraine prevention with topiramate in adults

Outcome	Daily dose of topiramate	Sample, reference	Rate, percent with drug [placebo]	Relative risk (95% CI)	Adjusted risk difference (95% CI)	Bayesian Odds ratio (2.5 to 97.5 percentile)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
≥50% reduction in monthly migraine days	**50 to 200mg/day**	**1,145[88, 186, 187]**	**41.8 [22.8]**	**1.8 (1.1 to 2.9)**	**0.18 (0.08 to 0.28)**		**5 (4 to 11)**	**182 (93 to 271)**	**High**
≥75% reduction in monthly migraine attack rate	**50 to 200mg/day**	**1,327[84, 85, 186, 187]**	**21.2 [9.9]**	**2.1 (1.6 to 2.8)**	**0.12 (0.02 to 0.22)**		**7 (4 to 48)**	**142 (21 to 262)**	**High**
≥75% reduction in monthly migraine days		**328[186, 187]**	**15.2 [9.2]**	**2.1 (1.6 to 2.9)**	**0.11 (0.02 to 0.19)**		**10 (6 to 27)**	**105 (37 to 173)**	**Moderate**
≥50% reduction in monthly migraine frequency (responder rate)	**100 mg/day**	**774[187-190]**	**44.1 [21.7]**	**2.0 (1.3 to 3.2)**	**0.26 (0.07 to 0.44)**	**3.1 (1.5 to 6.5)**	**4 (3 to 10)**	**250 (104 to 396)**	**High**
≥50% reduction in monthly migraine frequency (responder rate)	**200mg/day**	**746[84, 188, 190-192]**	**46.4 [24.2]**	**2.0 (1.3 to 3.0)**	**0.23 (0.12 to 0.33)**	**2.7 (1.7 to 4.5)**	**4 (3 to 8)**	**224 (123 to 325)**	**High**
≥50% reduction in monthly migraine frequency (responder rate)	**50mg/day**	**507[85, 188, 190, 191]**	**37.9 [21.2]**	**1.7 (1.2 to 2.6)**	**0.23 (0.06 to 0.41)**	**2.6 (1.4 to 5.4)**	**4 (2 to 22)**	**244 (46 to 441)**	**High**
Complete cure	50 to 200mg/day	893[84, 85, 187, 193]	5.2 [1.7]	2.2 (0.9 to 5.5)	0.03 (-0.02 to 0.07)	3.1 (0.8 to 13.1)			Moderate

Bold – significant at 95% confidence limit
CI – confidence interval

Table 4. Summarizing evidence about migraine prevention with topiramate in adults

Outcome	Sample, references	Conclusion	Strength of evidence
≥50% reduction in monthly migraine days	1145[88, 186, 187]	Topiramate was better than placebo in achieving ≥50 percent reduction in monthly migraine days	High
≥75% reduction in monthly migraine attack rate	1327[84, 85, 186, 187]	Topiramate was better than placebo in achieving ≥75 percent reduction in monthly migraine attack rate	High
≥75% reduction in monthly migraine days	328[186, 187]	Topiramate was better than placebo in achieving ≥75 percent reduction in monthly migraine days	Moderate
≥50% reduction in monthly migraine frequency (responder rate)	774[187-190]	Topiramate, 100 mg/day was better than placebo in achieving ≥50 percent reduction in monthly migraine frequency (responder rate)	High
≥50% reduction in monthly migraine frequency (responder rate)	746[84, 188, 190-192]	Topiramate, 200 mg/day was better than placebo in achieving ≥50 percent reduction in monthly migraine frequency (responder rate)	High
≥50% reduction in monthly migraine frequency (responder rate)	507[85, 188, 190, 191]	Topiramate, 50 mg/day was better than placebo in achieving ≥50 percent reduction in monthly migraine frequency (responder rate)	High
Complete cure	893[84, 85, 187, 193]	Topiramate was not better than placebo in achieving complete cure from migraine attacks	Moderate
≥50% reduction in monthly migraine frequency (responder rate)	1,439[188, 190, 191]	Increase in topiramate dose to 100 mg/day resulted in higher response rate (≥50 percent reduction in monthly migraine frequency) without additional benefit from increasing the dose to 200 mg/day	High

Table 5. Migraine prevention with divalproex vs. placebo in adults, results from randomized controlled clinical trials

Outcome	Daily dose	Reference	Sample	Rate, percent with divalproex [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
≥50% reduction in migraine headache rate	**Mean average dose 871 mg/d**	**Freitag, 2002[90]**	**239**	**40.7 [27.6]**	**8 (4 to 86)**	**131 (12 to 250)**	**Low**
≥ 50% reduction in migraine headache rate	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**47.1 [13.5]**	**3 (2 to 6)**	**336 (176 to 497)**	
≥50% reduction in migraine headache rate	**Mean**	**Pooled**	**346**	**43.0 [24.2]**	**4 (2 to 40)**	**226 (25 to 427)**	**Low**
50% improvement in migraine attacks impairing usual activities	**500 mg**	**Klapper, 1997[92]**	**60**	**57.8 [25.0]**	**3 (2 to 22)**	**311 (45 to 577)**	**Low**
50% improvement in migraine attacks impairing usual activities	1000 mg	Klapper, 1997[92]	58	37.2 [25.0]			Low
50% improvement in migraine attacks impairing usual activities	**1500 mg**	**Klapper, 1997[92]**	**59**	**54.5 [25.0]**	**4 (2 to 91)**	**279 (11 to 547)**	**Low**
50% improvement in migraine attacks necessitating symptomatic medication	**500 mg**	**Klapper, 1997[92]**	**60**	**42.2 [13.6]**	**3 (2 to 16)**	**289 (64 to 513)**	**Low**
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg	Klapper, 1997[92]	57	37.2 [13.6]			Low
50% improvement in migraine attacks necessitating symptomatic medication	**1500 mg**	**Klapper, 1997[92]**	**59**	**43.2 [13.6]**	**3 (2 to 14)**	**298 (73 to 524)**	**Low**
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	**500 mg**	**Klapper, 1997[92]**	**60**	**46.7 [18.2]**	**4 (2 to 58)**	**267 (17 to 516)**	**Low**
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1000 mg	Klapper, 1997[92]	58	41.9 [18.2]			Low
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	**1500 mg**	**Klapper, 1997[92]**	**59**	**50.0 [18.2]**	**3 (2 to 20)**	300 (49 to 551)	**Low**

Bold – significant at 95% confidence limit
CI – confidence level

Table 6. Migraine prevention with valproate vs. placebo, results from moderate risk of bias randomized controlled clinical trial,[93] (low strength of evidence due to risk of bias and imprecision)

Outcome	Daily dose	Events/ randomized with valproate	Events/ randomized with placebo	Rate, percent with valproate [placebo]	Relative risk (95% CI)	Absolute risk Difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Responders (Frequency of migraine days was reduced to ≥50%)	**1,000 mg to 1,500 mg per day**	**17/43**	**6/43**	**39.5 [14.0]**	**2.8 (1.2 to 6.5)**	**0.26 (0.08 to 0.43)**	**4 (2 to 13)**	**256 (77 to 435)**

Bold – significant at 95% confidence limit
CI – confidence level

Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials

Outcome	Active drug, Daily dose	Control drug, Daily dose	Reference Risk of bias	Sample	Rate, percent [control]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
≥50% reduction of frequency of attack	Propranolol 80 mg b.i.d.	Placebo	Tfelt-Hansen, 1984[97] Risk of bias Moderate	144	50.0 [25.0]	Not significant	Not significant	
≥50% reduction of frequency of attack	Propranolol 160 mg/d	Placebo	Diener, 2004[95] Risk of bias Low	193	43.1 [21.9]	Not significant	Not significant	
≥50% reduction of frequency of attack	Propranolol 80 mg	Placebo	Standnes, 1982[100] Risk of bias Moderate	38	52.0 [24.0]	Not significant	Not significant	
Responder (defined as patient preference)	Propranolol 80 or 160 mg	Placebo	Diamond, 1976[194] Risk of bias Moderate	166	41.0[20.5]	Not significant	Not significant	
≥50% reduction of frequency of attack	Propranolol 80 mg	Placebo	Weber, 1972[195] Risk of bias Moderate	19	62.5 [0.0]	2 (1 to 3)	625 (287 to 963)	
≥50% reduction of frequency of attack	**Propranolol**	**Placebo**	**Pooled Risk of bias Moderate**	**560**	**45.5 [21.0]**	**4 (3 to 6)**	**256 (158 to 353)**	**Low**
≥50% reduction of frequency of attack	Topiramate 100 mg/d	Propranolol 160 mg/d	Diener, 2004[95] Risk of bias Low	285	36.9 [43.1]	Not significant	Not significant	Low
≥50% reduction of frequency of attack	Topiramate 200 mg/d	Propranolol 160 mg/d	Diener, 2004[95] Risk of bias Low	288	34.7 [43.1]	Not significant	Not significant	Low
≥50% reduction of frequency of attack	Divalproex	Propranolol	Kaniecki, 1997[144] Risk of bias High	74	56.8 [54.1]	Not significant	Not significant	Insufficient
Patients responding with a ≥50% reduction in mean migraine days (month)	Divalproex	Propranolol	Kaniecki, 1997[144] Risk of bias High	74	56.8 [59.5]	Not significant	Not significant	Insufficient
≥50% reduction of migraine days	Propranolol 160 mg	Clonidine 100 µg	Kass, 1980[145] Risk of bias Moderate	46	56.5 [34.8]	Not significant	Not significant	Low
≥50% reduction of migraine attacks	Propranolol 80-120 mg Oral	Cinnarizine	Olerud, 1986[146] Risk of bias Low	28	7.1 [14.3]	Not significant	Not significant	Low

Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials (continued)

Outcome	Active drug, Daily dose	Control drug, Daily dose	Reference Risk of bias	Sample	Rate, percent [control]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
100% reduction of migraine attacks	**Propranolol 80-120 mg Oral**	**Cinnarizine 25-75 mg**	Olerud, 1986[146] **Risk of bias Low**	**28**	**50.0 [7.1]**	**2 (1 to 7)**	**429 (134 to 723)**	**Low**
100% reduction of migraine attacks	**Propranolol + Cinnarizine**	**Cinnarizine**	Olerud, 1986[146] **Risk of bias Low**	**28**	**85.7 [7.1]**	**1 (1 to 2)**	**786 (558 to 1013)**	**Low**
≥50% reduction of the sum of severity scores	Propranolol	Metoprolol	Kangasniemi, 1984[147] Risk of bias Moderate					
Responder of migraine days	Propranolol	Metoprolol	Gerber, 1991[148] Risk of bias Moderate					
	Propranolol	Metoprolol	Pooled Risk of bias Moderate	113	38.2 [50.0]	Not significant	Not significant	Low
≥50% reduction of frequency of distinct headache	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 80 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**93**	**9.1 [26.5]**	**-6 (-41 to -3)**	**-174 (-324 to -24)**	**Low**
≥50% reduction of frequency of distinct headache	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**91**	**9.1 [36.2]**	**-4 (-9 to -2)**	**-271 (-432 to -109)**	**Low**
≥50% reduction of frequency of distinct headache	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	93	11.4 [22.4]	Not significant	Not significant	Low
≥50% reduction of frequency of distinct headache	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**91**	**11.4 [38.3]**	**-4 (-10 to -2)**	**-269 (-437 to -102)**	**Low**
≥50% reduction of headache intensity	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	93	18.2 [28.6]	Not significant	Not significant	Low
≥50% reduction of headache intensity	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**91**	**18.2 [40.4]**	**-4 (-24 to -2)**	**-222 (-403 to -42)**	**Low**
≥50% reduction of headache intensity	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	93	22.7 [22.4]	Not significant	Not significant	Low
≥50% reduction of headache intensity	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**91**	**22.7 [44.7]**	**-5 (-32 to -2)**	**-220 (-408 to -31)**	**Low**

Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials (continued)

Outcome	Active drug, Daily dose	Control drug, Daily dose	Reference Risk of bias	Sample	Rate, percent [control]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
≥50% reduction of pain days	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	93	18.2 [18.4]	Not significant	Not significant	Low
≥50% reduction of pain days	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	Sudilovsky, 1987[149] **Risk of bias Moderate**	**91**	**18.2 [40.4]**	**-4 (-24 to -2)**	**-222 (-403 to -42)**	**Low**
≥50% reduction of pain days	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	93	20.5 [22.4]	Not significant	Not significant	Low
≥50% reduction of pain days	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 160 mg o.d.	Sudilovsky, 1987[149] Risk of bias Moderate	91	20.5 [38.3]	Not significant	Not significant	Low
≥50% reduction of frequency of attack	Nadolol 80 mg/daily (every morning + matching placebo tablet every night)	Propranolol 80 mg (40 mg twice daily)	Olerud, 1986[146] Risk of bias Moderate	28	38.5 [60.0]	Not significant	Not significant	Low
Completely relieved of migraine	Timolol	Placebo	Briggs, 1979[196]	28	14.3 [0.0]	Not significant	Not significant	Low
Responders (Patients with ≥50% reduction in headache frequency): to only one therapy	**Timolol**	Placebo	**Stellar, 1984[101]**	**94**	**53.2 [21.3]**	**3 (2 to 7)**	**319 (135 to 504)**	**Low**
≥50% reduction of frequency of attack	Timolol 10 mg b.i.d. (+ propranolol placebo)	Propranolol 80 mg b.i.d. (plus timolol placebo)	Tfelt-Hansen, 1984[97] Risk of bias Moderate					
≥50% reduction of frequency of attack	Timolol 10 mg + (propranolol placebo)	Propranolol 80 mg + (timolol placebo)	Standnes, 1982[100] Risk of bias Moderate					
≥50% reduction of frequency of attack	Timolol	Propranolol	Pooled Risk of bias Moderate	242	47.9 [50.4]	Not significant	Not significant	Low

Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials (continued)

Outcome	Active drug, Daily dose	Control drug, Daily dose	Reference Risk of bias	Sample	Rate, percent [control]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Responder of migraine days	**Propranolol Hydrochloride 80 mg / day (LD)**	**Nifedipine 20 mg/day (LD)**	**Gerber, 1991[148] Risk of bias Moderate**	**36**	**21.1 [0.0]**	**5 (2 to 81)**	**211 (12 to 409)**	**Low**
Responder of migraine days	Propranolol Hydrochloride 160 mg / day (HD)	Nifedipine 40 mg/day (HD)	Gerber, 1991[148] Risk of bias Moderate					
Drug efficacy: >50% improvement	Propranolol 60 mg TID	Nifedipine 30 mg TID	Albers, 1989[150] Risk of bias High					
>50% improvement	**Propranolol**	**Nifedipine**	**Pooled Risk of bias High**	**76**	**46.2 [18.9]**	**4 (2 to 11)**	**274 (89 to 458)**	**Low**
≥50% reduction of the number of days with headache	Propranolol 40 mg/d	Nortriptyline 20 mg/d	Domingues, 2009[152] Risk of bias Moderate	49	33.3 [39.3]	Not significant	Not significant	Low
Good response: fall in headache score (compared with placebo treatment) of ≥50%	Propranolol 80-240 mg/d	Amitriptyline 50-150 mg/d	Ziegler, 1987[151] Risk of bias Moderate	108	19.2 [21.4]	Not significant	Not significant	Low
>50% reduction of frequency of attack	Propranolol 80 mg twice a day	Femoxetine 200 mg twice a day	Kangasniemi, 1983[153] Risk of bias Moderate	29	20.0 [7.1]	Not significant	Not significant	Low
50% reduction of migraine attacks	Propranolol LA 80-120 mg	Propranolol: 80 mg/d+ Cinnarizine 25-75 mg/day	Olerud, 1986[146] Risk of bias Low	28	7.1 [0.0]	Not significant	Not significant	Low
75% reduction of migraine attacks	Propranolol LA 80-120 mg	Propranolol: 80 mg/d+ Cinnarizine 25-75 mg/day	Olerud, 1986[146] Risk of bias Low	28	35.7 [14.3]	Not significant	Not significant	Low
100% reduction of migraine attacks	**Propranolol LA (+placebo) 80-120 mg**	**Propranolol + Cinnarizine Propranolol: 80 mg/day; Cinnarizine 25-75 mg/d**	Olerud, 1986[146] **Risk of bias Low**	**28**	**50.0 [85.7]**	**-3 (-27 to -1)**	**-357 (-677 to -37)**	**Low**

Table 7. Migraine prevention with propranolol or timolol, results from randomized controlled clinical trials (continued)

Outcome	Active drug, Daily dose	Control drug, Daily dose	Reference Risk of bias	Sample	Rate, percent [control]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
≥50% reduction of the number of days with headache	Nortriptyline 20 mg/d	Propranolol + Nortriptyline	Domingues, 2009[152] Risk of bias Moderate	51	29.2 [37.0]	Not significant	Not significant	Low
≥50% reduction of the number of days with headache	Propranolol 40 mg/d	Propranolol + Nortriptyline	Domingues, 2009[152] Risk of bias Moderate	52	44.0 [37.0]	Not significant	Not significant	Low

Bold – significant at 95% confidence limit
CI – confidence interval

Table 8. Reduction in frequency of migraine attack by ≥50% from baseline with timolol 10mg twice a day (attributable events based on meta-analysis of randomized controlled clinical trials)

Sample size, Reference	Rate, percent with active drug	Rate, percent with placebo	Pooled relative risk (95% CI)	Pooled absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
276[97, 100, 101]	49.4	23.3	**2.1 (1.5 to 3.1)**	**0.3 (0.2 to 0.4)**	**4 (3 to 6)**	**265 (154 to 377)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 9. Efficacy of off- label antiepileptic drugs vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials

Definition outcomes	Active drugs, daily dose	Reference Risk of bias	Sample	Events/ randomized with active drug	Events/ randomized with placebo	Rate, percent with active drug [placebo]	Relative risk (95% CI)	Absolute risk Difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Response (≥50% reduction in attack frequency)	Acetazolamide 500 mg (250 twice daily)	Vahedi, 2002[197] Risk of bias Low	53.00	8/26	9/27	30.8 [33.3]	0.9 (0.4 to 2.0)	-0.03 (-0.28 to 0.23)	NS	NS	Low
Improvement marked to complete control	**Carbamazepine One tablet 3 times a day**	**Rompel, 1970[198] Risk of bias Moderate**	**96.00**	**26/48**	**5/48**	**54.2 [10.4]**	**5.2 (2.2 to 12.4)**	**0.44 (0.27 to 0.60)**	**2 (2 to 4)**	**438 (272 to 603)**	**Low**
≥50% reduction in the 4 week migraine headache rate	**Gabapentin Titrated up to 2400 mg daily**	**Mathew, 2001[199] Risk of bias Moderate**	**143.00**	**26/98**	**5/45**	**26.5 [11.1]**	**2.4 (1.0 to 5.8)**	**0.15 (0.03 to 0.28)**	**6 (4 to 36)**	**154 (27 to 281)**	**Low**
Decrease of the frequency migraine attacks	Gabapentin 900 mg (300 x 3)	Wessely, 1987[200] Risk of bias Moderate	45.00	18/23	12/22	78.3 [54.5]	1.4 (0.9 to 2.2)	0.24 (-0.03 to 0.50)	NS	NS	Low
≥ 50% reduction of number of migraine	Oxcarbazepine Maximum tolerated dose of 1,200 mg/day	Silberstein, 2008[201] Risk of bias Low	170.00	28/85	31/85	32.9 [36.5]	0.9 (0.6 to 1.4)	-0.04 (-0.18 to 0.11)	NS	NS	Low
Clinical Global Impression: "Very much improved“	Oxcarbazepine Maximum tolerated dose of 1,200 mg/day	Silberstein, 2008[201] Risk of bias Low	170.00	53/85	54/85	62.4 [63.5]	1.0 (0.8 to 1.2)	-0.01 (-0.16 to 0.13)	NS	NS	Low

NS – not significant
Bold – significant at 95% confidence limit
CI – confidence level

Table 10. Efficacy of beta blockers for migraine prevention in adults, evidence from randomized controlled clinical trials

Definition of the outcome	Name of drug in active group	Reference	Sample size	Rate of outcome percent with drug [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Better during the period of the trial	Alprenolol	Ekbom, 1975[108]	66	33.3 [36.4]	Not significant	Not significant	Low
Reduction of number of attacks by ≥50%	**Atenolol**	**Forssman, 1982-83[106, 202]**	**48**	**33.3 [0.0]**	**3 (2 to 7)**	**333 (140 to 527)**	**Low**
Marked reduction in migraine attacks	**Metoprolol**	**Kangasneimi, 1987[103]** **Andersson, 1983[104]**	**225**	**39.9 [19.4]**	**5 (3 to 11)**	**204 (88 to 321)**	**Moderate**
Treatment successful: Frequency	**Nadolol**	**Freitag, 1984[107]**	**32**	**25.0 [0.0]**	**4 (2 to 45)**	**250 (22 to 478)**	**Low**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 11. Migraine prevention with antiadrenergics and antidepressant medications, results from randomized controlled clinical trials

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
≥50% reduction in headache index	**Clonidine 25 micrograms 3 times daily**	**Placebo**	**Schachtel, 1988[203] Risk of bias Moderate**	**10/30**	**0/30**	**33.3 [0.0]**	**21.0 (1.3 to 342.9)**	**0.33 (0.16 to 0.51)**	**3 (2 to 6)**	**333 (161 to 506)**
75% or better improvement in headache	**Amitriptyline 50 mg - 100mg**	**Placebo**	**Couch[110] Risk of bias Moderate**	**16/37**	**7/36**	**43.2 [19.4]**	**2.2 (1.0 to 4.8)**	**0.24 (0.03 to 0.44)**	**4 (2 to 31)**	**238 (33 to 443)**
Improvement of M score >50%	**Amitriptyline 50 mg - 100mg**	**Placebo**	**Couch, 1979[204] Risk of bias Moderate**	**26/55**	**18/61**	**47.3 [29.5]**	**1.6 (1.0 to 2.6)**	**0.18 (0.00 to 0.35)**	**6 (3 to 336)**	**178 (3 to 352)**
Excellent improvement	Fluoxetine 20 mg - 40 mg every day	Placebo	Adly, 1992[111] Risk of bias Moderate	6/16	1/16	37.5 [6.3]	6.0 (0.8 to 44.4)	**0.31 (0.05 to 0.58)**	**3 (2 to 21)**	**313 (47 to 578)**
Good response: fall in headache score (compared with placebo treatment) of ≥50%	Amitriptyline 50-150 mg	Propranolol 80-240 mg/d	Ziegler, 1987[151] Risk of bias Moderate	10/54	12/54	18.5 [22.2]	0.8 (0.4 to 1.8)	-0.04 (-0.19 to 0.11)		
≥50% improvement in attack frequency	Femoxetine 200 mg daily 1st week and 400 mg daily after	Propranolol 80 mg daily for 1st week and 160 mg daily later	Kangasniemi, 1983[153] Risk of bias Moderate	3/11	1/13	27.3 [7.7]	3.5 (0.4 to 29.4)	0.20 (-0.10 to 0.50)		
≥50% reduction of the number of days with headache	Nortriptyline 20 mg/d	Propranolol 40 mg/d	Domingues, 2009[152] Risk of bias Moderate	7/24	11/25	29.2 [44.0]	0.7 (0.3 to 1.4)	-0.15 (-0.41 to 0.12)		
≥ 50% reduction of the number of days with headache	Nortriptyline 20 mg/d	Propranolol + nortriptyline	Domingues, 2009[152] Risk of bias Moderate	7/24	10/27	29.2 [37.0]	0.8 (0.4 to 1.7)	-0.08 (-0.34 to 0.18)		

Table 11. Migraine prevention with antiadrenergics and antidepressant medications, results from randomized controlled clinical trials (continued)

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Overall 50% responder rate of the number of headache days	Tonabersat 20 mg - 40 mg	Placebo	Goadsby, 2009[112] Risk of bias Low	35/59	32/65	59.3 [49.2]	1.2 (0.9 to 1.7)	0.10 (-0.07 to 0.28)		
Overall 50% responder rate of the number of migraine attacks	**Tonabersat 20 mg - 40 mg**	**Placebo**	**Goadsby, 2009[112] Risk of bias Low**	**37/59**	**29/65**	**62.7 [44.6]**	**1.4 (1.0 to 2.0)**	**0.18 (0.01 to 0.35)**	**6 (3 to 121)**	**181 (8 to 354)**
Excellent improvement	Venlafaxine 75 mg	Placebo	Ozyalcin, 2005[113] Risk of bias Moderate	3/20	0/19	15.0[0.0]	6.7 (0.4 to 121.1)	0.15 (-0.02 to 0.32)		
Excellent improvement	**Venlafaxine 150 mg**	**Placebo**	**Ozyalcin, 2005[113] Risk of bias Moderate**	**9/21**	**0/19**	**42.9 [0.0]**	**17.3 (1.1 to 278.0)**	**0.43 (0.21 to 0.65)**	**2 (2 to 5)**	**429 (211 to 647)**
Improvement	Venlafaxine 75 mg	Placebo	Ozyalcin, 2005[113] Risk of bias Moderate	14/20	8/19	70.0 [42.1]	1.7 (0.9 to 3.0)	0.28 (-0.02 to 0.58)		
improvement	**Venlafaxine 150 mg**	**Placebo**	**Ozyalcin, 2005[113] Risk of bias Moderate**	**16/21**	**8/19**	**76.2 [42.1]**	**1.8 (1.0 to 3.2)**	**0.34 (0.05 to 0.63)**	**3 (2 to 19)**	**341 (54 to 628)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 12. Migraine prevention in adults with calcium channel antagonists and systemic drug montelukast, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
50% improvement	**Nimodipine 30 mg four times daily**	**Placebo**	**Havanka-Kanniainen, 1985[114] Risk of bias Moderate**	**10/33**	**0/33**	**30.3 [0.0]**	**21.0 (1.3 to 344.3)**	**0.30 (0.14 to 0.46)**	**3 (2 to 7)**	**303 (143 to 464)**
Patients with 1 migraine attack in 4 weeks	Nimodipine 40 mg tid	Placebo	Gelmers, 1983[115] Risk of bias Moderate	8/30	4/30	26.7 [13.3]	2.0 (0.7 to 5.9)	0.13 (-0.07 to 0.33)		
Patients without migraine attacks	**Nimodipine 40 mg tid**	**Placebo**	**Gelmers, 1983[115] Risk of bias Moderate**	**15/30**	**2/30**	**50.0 [6.7]**	**7.5 (1.9 to 30.0)**	**0.43 (0.23 to 0.63)**	**2 (2 to 4)**	**433 (233 to 633)**
≥50% decrease in monthly migraine attacks	Montelukast 20 mg	Placebo	Brandes, 2004[129] Risk of bias Low	14/93	9/84	15.4 [10.3]	1.4 (0.6 to 3.1)	0.04 (-0.05 to 0.14)		

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 13. Migraine prevention in adults with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
No headaches during drug administration	Captopril 50 mg 3 times/day	Placebo	Minervini, 1987[120] Risk of bias Low	8/12	0/12	66.7 [0.0]	17.0 (1.1 to 265.0)	0.67 (0.39 to 0.95)	1 (1 to 3)	667 (388 to 946)
Migraine index improved 50%	Captopril 50 mg 3 times/day	Placebo	Minervini, 1987[120] Risk of bias Low	12/12	1/12	100.0 [8.3]	8.3 (1.8 to 37.7)	0.92 (0.71 to 1.12)	1 (1 to 1)	917 (714 to 1119)
Reduction by≥ 50% in symptoms for hours with headache	Lisinopril 10 mg for 1 week, then 20 mg for 11 weeks	Placebo	Schrader, 2001[119] Risk of bias Low	10/60	0/60	16.7 [0.0]	21.0 (1.3 to 350.5)	0.17 (0.07 to 0.26)	6 (4 to 14)	167 (69 to 264)
Reduction by ≥50% in symptoms of days with headache	Lisinopril 10 mg for 1 week, then 20 mg for 11 weeks	Placebo	Schrader, 2001[119] Risk of bias Low	13/60	0/60	21.7 [0.0]	27.0 (1.6 to 444.1)	0.22 (0.11 to 0.32)	5 (3 to 9)	217 (110 to 323)
Reduction by ≥50%t in symptoms for days with migraine	Lisinopril 10 mg for 1 week, then 20 mg for 11 weeks	Placebo	Schrader, 2001[119] Risk of bias Low	14/60	0/60	23.3 [0.0]	29.0 (1.8 to 475.4)	0.23 (0.12 to 0.34)	4 (3 to 8)	233 (124 to 343)
Reduction by ≥50% in symptoms for headache severity index	Lisinopril 10 mg for 1 week, then 20 mg for 11 weeks	Placebo	Schrader, 2001[119] Risk of bias Low	15/60	0/60	25.0 [0.0]	31.0 (1.9 to 506.6)	0.25 (0.14 to 0.36)	4 (3 to 7)	250 (138 to 362)
Responders (as defined by ≥50% reduction) in headache days	Candesartan 16 mg	Placebo	Tronvik, 2003[121] Risk of bias Low	18/60	1/60	30.0 [1.7]	18.0 (2.5 to 130.6)	0.28 (0.16 to 0.40)	4 (2 to 6)	283 (163 to 404)

Table 13. Migraine prevention in adults with angiotensin converting enzyme inhibitors and angiotensin II receptor antagonists, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision (continued)

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Responders (as defined by ≥50% reduction) in headache hours	**Candesartan 16 mg**	**Placebo**	**Tronvik, 2003[121] Risk of bias Low**	**20/60**	**1/60**	**33.3 [1.7]**	**20.0 (2.8 to 144.3)**	**0.32 (0.19 to 0.44)**	**3 (2 to 5)**	**317 (193 to 440)**
Responders (as defined as ≥ 50% in migraine days	**Candesartan 16 mg**	**Placebo**	**Tronvik, 2003[121] Risk of bias Low**	**23/60**	**2/60**	**38.3 [3.3]**	**11.5 (2.8 to 46.6)**	**0.35 (0.22 to 0.48)**	**3 (2 to 5)**	**350 (219 to 481)**
Responders (as defined by ≥50% reduction) in headache severity index	**Candesartan 16 mg**	**Placebo**	**Tronvik, 2003[121] Risk of bias Low**	**23/60**	**2/60**	**38.3 [3.3]**	**11.5 (2.8 to 46.6)**	**0.35 (0.22 to 0.48)**	**3 (2 to 5)**	**350 (219 to 481)**
Responders (as defined by ≥50% reduction)in migraine hours	**Candesartan 16 mg**	**Placebo**	**Tronvik, 2003[121] Risk of bias Low**	**26/60**	**1/60**	**43.3 [1.7]**	**26.0 (3.6 to 185.5)**	**0.42 (0.29 to 0.55)**	**2 (2 to 3)**	**417 (287 to 546)**
Responder (≥50% reduction in migraine days)	Telmisartan 80 mg	Placebo	Diener, 2009[122] Risk of bias High	16/48	11/47	33.3 [23.4]	1.4 (0.7 to 2.7)	0.10 (-0.08 to 0.28)		

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 14. Migraine prevention in adults with ergot alkaloids, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
No (0) migraine attacks	Dihydroergotamine 10 mg daily (5 mg capsule x 2)	Placebo	Pradalier, 2004[128] Risk of bias Low	53/184	48/200	28.8[24.0]	1.2 (0.9 to 1.7)	0.05 (-0.04 to 0.14)		
Response (≥50% reduction in migraine attack frequency)	Dihydroergotamine 10 mg daily (5 mg capsule x 2)	Placebo	Pradalier, 2004[128] Risk of bias Low	112/184	112/200	60.9[56.0]	1.1 (0.9 to 1.3)	0.05 (-0.05 to 0.15)		
≥50% reduction in frequency of attacks	Lisuride Hydrogen Maleate 25 mcg tid	Methysergide 2 mg tid	Herrmann, 1977[205] Risk of bias Moderate	69/130	63/123	53.1[51.2]	1.0 (0.8 to 1.3)	0.02 (-0.10 to 0.14)		

CI – confidence interval

Table 15. Migraine prevention in adults with nonsteroid anti-inflammatory drugs, results from randomized controlled clinical trials, low strength of evidence due to risk of bias and imprecision of the estimates

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Greater than 50% improvement on headache unit index	Fenoprofen 200 mg TID	Placebo	Diamond, 1987[206] Risk of bias moderate	7/32	7/34	21.9 [20.6]	1.1 (0.4 to 2.7)	0.01 (-0.18 to 0.21)		
Greater than 50% improvement in relief medication index	Fenoprofen 200 mg TID	Placebo	Diamond, 1987[206] Risk of bias moderate	9/33	8/34	27.3 [23.5]	1.2 (0.5 to 2.6)	0.04 (-0.17 to 0.25)		
≥50% improvement on corrected headache unit index	Fenoprofen 200 mg TID	Placebo	Diamond, 1987[206] Risk of bias moderate	11/34	11/35	32.4 [31.4]	1.0 (0.5 to 2.1)	0.01 (-0.21 to 0.23)		
≥50% improvement on headache unit index	Fenoprofen 600 mg TID	Placebo	Diamond, 1987[206] Risk of bias moderate	13/36	7/34	36.1 [20.6]	1.8 (0.8 to 3.9)	0.16 (-0.05 to 0.36)		
≥50% improvement on corrected headache unit index	**Fenoprofen 600 mg TID**	**Placebo**	**Diamond, 1987[206] Risk of bias moderate**	**16/27**	**11/35**	**59.3 [31.4]**	**1.9 (1.1 to 3.4)**	**0.28 (0.04 to 0.52)**	**4 (2 to 27)**	**278 (37 to 519)**
≥50% improvement in relief medication index	**Fenoprofen 600 mg TID**	**Placebo**	**Diamond, 1987[206] Risk of bias moderate**	**21/38**	**8/34**	**55.3 [23.5]**	**2.3 (1.2 to 4.6)**	**0.32 (0.10 to 0.53)**	**3 (2 to 10)**	**317 (104 to 530)**
≥50% reduction in migraine duration	**Flurbiprofen 100 mg twice daily**	**Placebo**	**Solomon, 1993[207] Risk of bias moderate**	**7/20**	**1/20**	**35.0 [5.0]**	**7.0 (0.9 to 51.8)**	**0.30 (0.07 to 0.53)**	**3 (2 to 14)**	**300 (70 to 530)**

Table 15. Migraine prevention in adults with nonsteroid anti-inflammatory drugs, results from randomized controlled clinical trials, low strength of evidence due to risk of bias and imprecision of the estimates (continued)

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Decrease in migraine frequency	**Flurbiprofen 100 mg twice daily**	**Placebo**	**Solomon, 1993[207] Risk of bias moderate**	**16/23**	**7/23**	**69.6 [30.4]**	**2.3 (1.2 to 4.5)**	**0.39 (0.13 to 0.66)**	**3 (2 to 8)**	**391 (125 to 657)**
Headache free	Indomethacin 25 mg three times a day	Placebo	Anthony, 1968[208] Risk of bias moderate	1/19	2/19	5.3 [10.5]	0.5 (0.0 to 5.1)	-0.05 (-0.22 to 0.12)		
More than half improved	Indomethacin 25 mg three times a day	Placebo	Anthony, 1968[208] Risk of bias moderate	6/19	5/19	31.6 [26.3]	1.2 (0.4 to 3.3)	0.05 (-0.24 to 0.34)		
Subjective "clear improvement"	**Aspirin 325 mg BID**	**Placebo**	**Masel, 1980[209] Risk of bias Moderate**	**17/40**	**1/40**	**42.5 [2.5]**	**17.0 (2.4 to 121.7)**	**0.40 (0.24 to 0.56)**	**3 (2 to 4)**	**400 (239 to 561)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 16. Comparative effectiveness of topiramate for migraine prevention in adults, individual randomized controlled clinical trials

Definition of the outcome	Control drug	Reference	Sample	Conclusion	Strength of evidence
≥50% reduction in mean monthly total headache days	Amitriptyline	Dodick, 2009[137]	347	Topiramate was more effective than amitriptyline in reducing monthly headache days by ≥50%	Low
≥50% reduction in mean monthly migraine days	Amitriptyline	Dodick, 2009[137]	347	Topiramate and amitriptyline had similar effect on reducing monthly migraine days by ≥50%	Low
Responder rate (≥50% reduction in monthly migraine frequency)	Lamotrigine	Gupta, 2007[138]	120	Topiramate and lamotrigine had similar effect on reducing monthly migraine frequency by ≥50%	Low
Headache intensity (≥50% reduction in mean migraine intensity)	Lamotrigine	Gupta, 2007[138]	120	Topiramate was more effective than lamotrigine in reducing monthly headache intensity by ≥50%	Low
Migraine frequency of less than 50% of the basal frequency	Levetiracetam	de Tommaso, 2007[141]	28	Migraine frequency of less than 50% of the basal frequency did not differ with topiramate and levetiracetam	Low
Reduction by ≥ 50% in days with headache	Valproate (slow-release)	Bartolini, 2005[140]	44	Reduction by ≥ 50% in days with headache did not differ with topiramate and valproate	Low
Decrease in headache frequency by ≥50%	Zonasamide	Mohammadianinejad, 2011[139]	80	Decrease in headache frequency by ≥50% did not differ with topiramate and zonasamide	Low

Table 17. Migraine prevention with valproate (600mg/day) vs. cinnarizine (75mg/day) in adults, results from low risk of bias randomized controlled clinical trial[143] (strength of evidence is low due to imprecision of estimate)

Outcome	Events/randomized with valproate	Events/randomized with cinnarizine	Rate, percent with valproate [Cinnarizine]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Responders (decreased in attack frequency by ≥ 50% as compared to run-in period)	37/67	41/58	55.2 [70.7]	0.8 (0.6 to 1.0)	-0.15 (-0.32 to 0.01)

CI – confidence interval

Table 18. Comparative effectiveness of beta blockers for migraine prevention in adults

Definition of the outcome	Reference	Active drug	Control drug	Sample	Rate of outcome in active group [rate of outcome in control group] percent	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Reduction of frequency of attacks by ≥50%	Worz, 1992[154]	Metoprolol	Bisoprolol	250	8.8 [9.6]	Not significant	Not significant	Low
Responder rate (≥50% decrease in number of attacks from baseline to endpoint)	Schellenberg, 2008[156]	Metoprolol	Nebivolol	30	57.0 [50.0]	Not significant	Not significant	Low
Reduction of attacks by ≥50%	**Grotemeyer, 1990[157]**	**Metoprolol**	**Acetylsalicylic acid**	**56**	**50.0 [10.7]**	**3 (2 to 6)**	**393 (175 to 611)**	Low
Responder rate (Reduction in the number of migraine attacks by ≥50%)	**Diener, 2001[158]**	**Metoprolol**	**Acetylsalicylic acid, 1500 mg/day**	**270**	**29.6 [45.2]**	**-6 (-24 to -4)**	**-156 (-269 to -42)**	Low
Reduction of ≥50% in the number of migraine days	Louis, 1985[159]	Metoprolol	Clonidine	62	32.3 [25.8]	Not significant	Not significant	Low
Subjective therapeutic evaluation: Marked or moderate	Louis, 1985[159]	Metoprolol	Clonidine	62	71.0 [48.4]	Not significant	Not significant	Low

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 19. Comparative effectiveness of antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial[165]

Definition of the outcome	Active treatment	Control treatment	Sample	Rate ,% with active vs. control treatment	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
>60% reduction in HI in last 4 weeks of treatment phase	**Spinal manipulation**	**Amitriptyline 100 mg/day**	**147**	**22.1 [48.6]**	**-4 (-9 to -2)**	**-265 (-414 to -116)**	**Low**
>60% reduction in HI during the 4-week post-treatment followup phase	Spinal manipulation	Amitriptyline 100 mg/day	147	22.1 [15.7]	NS	NS	Low
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal manipulation	Spinal manipulation + amitriptyline 100 mg/day	148	40.3 [40.8]	NS	NS	Low
Reduction in HI from baseline during the post-treatment followup period	**Spinal manipulation**	**Spinal manipulation + amitriptyline 100 mg/day**	**148**	**41.6 [25.4]**	**6 (3 to 80)**	**162 (13 to 312)**	**Low**
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal manipulation	Spinal manipulation + amitriptyline 100 mg/day	148	40.3 [40.8]	NS	NS	Low
Reduction in HI from baseline during the post-treatment followup period	**Spinal manipulation**	**Spinal manipulation + amitriptyline 100 mg/day**	**148**	**41.6 [25.4]**	**6 (3 to 80)**	**162 (13 to 312)**	**Low**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 20. Comparative effectiveness and safety of beta blockers combined with behavioral therapy (orientation +relaxation training; migraine warning signs and triggers; effectively using migraine medication, and reducing impact of migraines; stress management or biofeedback training; migraine management plan) for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[167]

Outcome	Name of drug in active group/exposure level	Name of drug in control group/reference exposure level	N	Rate % in active group [control group]	Number needed to Treat (95% CI)	Attributable events (95% CI)	Strength of evidence
Dropped due to side effects	Behavioral migraine management + propranolol/nadolol	Placebo	90	8.7 [9.1]	NS	NS	Low
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + propranolol/nadolol**	**Placebo**	**90**	**76.8 [40.0]**	**3 (2 to 6)**	**387 (157 to 618)**	**Low**
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + placebo	Propranolol/nadolol	108	34.5 [34.0]	NS	NS	Low
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + propranolol/nadolol**	**Propranolol/nadolol**	**122**	**76.8 [34.0]**	**2 (2 to 4)**	**428 (267 to 590)**	**Low**
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + placebo**	**Behavioral migraine management + Propranolol/nadolol**	**124**	**34.5 [76.8]**	**-2 (-4 to -2)**	**-423 (-583 to -262)**	**Low**
Dropped due to side effects	Behavioral migraine management + placebo	Propranolol/nadolol	108	9.1 [13.2]	NS	NS	Low
Dropped due to side effects	Behavioral migraine management + propranolol/nadolol	Propranolol/nadolol	122	8.7 [13.2]	NS	NS	Low
Dropped out due to side effects	Behavioral migraine management +placebo	Behavioral migraine management + Propranolol/nadolol	124	9.1 [8.7]	NS	NS	Low

Bold – significant at 95% confidence limit
CI - confidence interval

Table 21. Dose response reduction in migraine attacks by ≥50% from baseline with topiramate in adults

Reference Risk of bias	Topiramate daily doses	Events/randomized with drug and placebo	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events (95% CI)
Brandes, 2004[188] Risk of bias Low	100mg vs. 50mg/day	60/122 47/120	1.3 (0.9 to 1.7)	0.10 (-0.02 to 0.23)		
Silberstein, 2003[191] Risk of bias Moderate	**100mg vs. 50mg/day**	**68/125 41/117**	**1.5 (1.1 to 2.1)**	**0.19 (0.07 to 0.31)**	**5 (3 to 15)**	**189 (67 to 312)**
Silberstein, 2004[190] Risk of bias Low	**100mg vs. 50mg/day**	**69/128 45/125**	**1.5 (1.1 to 2.0)**	**0.18 (0.06 to 0.30)**	**6 (3 to 17)**	**179 (58 to 300)**
Pooled Risk of bias	**100mg vs. 50mg/day**	**196/375 133/362**	**1.4 (1.2 to 1.7)**	**0.16 (0.09 to 0.23)**	**6 (4 to 12)**	**157 (86 to 228)**
Brandes, 2004[188] Risk of bias Low	100mg vs. 50mg/day	57/121 47/120	1.2 (0.9 to 1.6)	0.08 (-0.05 to 0.20)		
Silberstein, 2003[191] Risk of bias Moderate	**200mg/day vs. 50mg/day**	**58/112 41/117**	**1.5 (1.1 to 2.0)**	**0.17 (0.04 to 0.29)**	**6 (3 to 24)**	**167 (41 to 294)**
Silberstein, 2004[190] Risk of bias Low	**200mg/day vs. 50mg/day**	**61/117 45/125**	**1.4 (1.1 to 1.9)**	**0.16 (0.04 to 0.29)**	**6 (4 to 26)**	**161 (38 to 285)**
Pooled Risk of bias	**200mg/day vs. 50mg/day**	**176/350 133/362**	**1.4 (1.2 to 1.6)**	**0.14 (0.06 to 0.21)**	**7 (5 to 16)**	**136 (64 to 208)**
Brandes, 2004[188] Risk of bias Low	200mg/day vs. 100mg/day	57/121 60/122	1.0 (0.7 to 1.2)	-0.02 (-0.15 to 0.11)		
Silberstein, 2003[191] Risk of bias Moderate	200mg/day vs. 100mg/day	58/112 68/125	1.0 (0.8 to 1.2)	-0.02 (-0.15 to 0.11)		
Silberstein, 2004[190] Risk of bias Low	200mg/day vs. 100mg/day	61/117 69/128	1.0 (0.8 to 1.2)	-0.02 (-0.14 to 0.11)		
Pooled Risk of bias	200mg/day vs. 100mg/day	176/350 196/375	1.0 (0.8 to 1.1)	-0.02 (-0.09 to 0.05)		

Bold – significant at 95% confidence limit
CI – confidence interval

Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?

Bothersome adverse effects leading to treatment discontinuation were examined in 52 RCTs with 28 different drugs from eight drug classes. Individual head-to-head RCTs provided low strength of evidence that botulinum toxin, topiramate, acetazolamide, and lamotrigine increased rates of treatment discontinuation due to adverse effects more often than placebo (Table A in the Executive Summary). Bayesian network meta-analysis demonstrated that topiramate, divalproex, off-label antiepileptics, antidepressants, and ergot alkaloids increased rates of bothersome adverse effects leading to treatment discontinuation. Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Nonrandomized studies suggested that 10 to 20 percent of patients discontinued antiepileptic drug treatments at one year or longer of followup (Appendix Table D122).

Muscle Relaxants

Botulinum Toxin

Fifteen RCTs of 4,566 adults examined the safety of botulinum toxin for migraine prevention in adults (Appendix Table D12). Botulinum toxin resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo (moderate strength of evidence) (Table 22). Pooled analyses demonstrated that per 1,000 patients treated, 155 experienced adverse effects and 26 discontinued treatments due to bothersome adverse effects (Table 22). The results were robust and remained significant with different methods of pooling (Appendix Tables D123 and D124).

Among individual adverse effects, neck pain and muscle weakness were the most common (Table 22). Increase in risk of adverse effects with botulinum toxin was lower in trials with higher placebo rates of adverse effects (Table 23). Increase in risk of adverse effects was dose responsive (Appendix Table D125). Patients experienced eyelid edema with 50U of botulinum toxin more often than with 7.5 or 25U.[169] Higher doses of 150 to 225U of botulinum toxin resulted in greater risk of blepharoptosis, muscle weakness, and neck rigidity (Appendix Table D126).

Antiepileptics

Topiramate

Seventeen RCTs and one pooled analysis of individual patient data that examined safety with topiramate versus placebo for migraine prevention in adults (Appendix Table D127). Trials enrolled 5,423 adults 41±3 years old. Women constituted 78 percent of all enrollees. Most trials were funded by industry and reported conflict of interest by principal investigators (Appendix Table D127). All trials were double blind (Appendix Table D128).

Patients stopped taking topiramate more often than placebo because of intolerable adverse effects (Table 24). Topiramate in doses of 100 and 200 mg/day (but not 50 mg/day) resulted in

treatment discontinuation due to adverse effects more often than placebo (Appendix Table D129). Compared to placebo, topiramate more often resulted in bothersome insomnia, paresthesia, cognitive deficits, and fatigue leading to withdrawal (Appendix Table D129). Pooled estimates were consistent with imprecision that decreased strength of evidence (Appendix Table D130). Per 1,000 treated, topiramate resulted in bothersome adverse effects leading to treatment discontinuation in 36 (with 100 mg/day) or 146 (with 200 mg/day) patients (Table 25). Published pooled analysis of individual patient data demonstrated topiramate discontinuation due to anorexia, anxiety, depression, hypoesthesia, and nausea (Appendix Table D131).[210]

Topiramate increased risk of individual adverse effects. Individual RCTs reported small numbers of events. Pooled analyses demonstrated a statistically significant increase in risk of any adverse effect, abdominal pain, anorexia, paresthesia, cognitive difficulties, diarrhea, dry mouth, fatigue, nausea, taste alteration or perversion, abnormal vision, and weight loss (Appendix Table D132). Topiramate caused adverse effects in one patient for every eight treated. Taste alteration and paresthesia were the most common adverse effects (>300 cases per 1,000 treated) (Table 26).

Risk of adverse effects was dose responsive according to the published pooled analyses of individual patient data (Appendix Table D133).[210] Larger doses of topiramate increased risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal, dry mouth, marked anorexia, paresthesia or fatigue, mood problems, nausea, and weight loss.[210]

Divalproex

Adverse effects with divalproex versus placebo were examined in three RCTs of 590 adults that examined efficacy of divalproex for migraine prevention in adults (Table 27 and Appendix Table D29). All three RCTs were funded by industry (Appendix Table D30) and all were double blind (Appendix Table D31).

Treatment discontinuation due to adverse effects did not differ with divalproex versus placebo (two RCTs of 239 patients, low strength of evidence) (Appendix Table D134).[90, 91] Divalproex caused alopecia, asthenia, nausea, and tremor more often than placebo) (Table 27). Strength of evidence was low because of risk of bias and imprecision of the treatment effects (Appendix Table D135). Larger doses of divalproex did not increase risk of bothersome adverse effects leading to treatment discontinuation (Appendix Table D136).[92] Larger doses of divalproex increased risk of nausea and tremor (Appendix Table D137).[92]

Valproate

Adverse effects of valproate were examined in two small double blind RCTs of 75 adults that examined efficacy of valproate for migraine prevention in adults (Table 28 and Appendix Tables D29-D31).

Treatment discontinuation due to adverse effects did not differ with valproate versus placebo (two RCT of 32 patients, low strength of evidence) (Appendix Table D138).[94] Rates of combined adverse effects did not differ between valproate and placebo (Appendix Table D139).

Beta Blockers

Propranolol (one RCT of 166 adults)

Nineteen publications of 18 RCTs examined safety with propranolol versus placebo (Table 29 and Appendix Table D35). All trials were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D37). Propranolol did not cause

bothersome adverse effects leading to treatment discontinuation more often than placebo (low strength of evidence) (Appendix Table D140).[194]

Propranolol resulted in adverse effects more often than placebo (pooled 92 attributable events per 1000 treated 95 percent CI, 12 to 172). Among individual adverse effects, propranolol resulted in diarrhea (pooled 89 attributable events per 1,000 treated; 95 percent CI, 14 to164), fatigue (129 attributable events per 1,000 treated; 95 percent CI, 56 to 202), and nausea (pooled 52 attributable events per 1,000 treated 95 percent CI, 14 to 91) more often than placebo.

Timolol

Treatment discontinuation due to bothersome adverse effects did not differ with timolol and placebo (low strength of evidence from individual RCTs) (Table 29 and Appendix Tables D141 and D142). Timolol did not cause any adverse effects more often than placebo (Appendix Tables D143 and D144).

Off-label Drugs

Antiepileptics

Eight RCTs examined safety of six off label antiepileptic drugs including acetazolamide, gabapentin, vigabatrin, oxcarbazepine, carbamazepin, and lamotrigen (Appendix Table D40). All trials were double blind (Appendix Table D42). Individual RCTs demonstrated that acetazolamide[197] and lamotrigen[211] resulted in treatment discontinuation due to bothersome adverse effects was more often than placebo (Table 30). Rate of treatment discontinuation due to adverse effects did not differ between carbamazepin, gabapentin, and oxcarbazepine and placebo (Table 30).

Acetazolamide

Acetazolamide caused paresthesia, drowsiness, memory impairment, malaise, and fasciculation more often than placebo (Appendix Table D145).[197]

Carbamazepin

Carbamazepin caused adverse effects necessitating reduction of dosage, vertigo, and drowsiness more often than placebo (Appendix Table D146).[198]

Gabapentin

Gabapentin caused somnolence and dizziness more often than placebo (Appendix Table. D147).[199]

Lamotrigen

Lamotrigen caused treatment discontinuation due to adverse effects including rash more often than placebo (Appendix Table D148).[211] A fixed dose of 200 mg/day of lamotrigen caused skin rash more often than placebo in contrast with gradually escalated dose of lamotrigen starting with 25 mg/day that did not cause skin rash.[211]

Oxcarbazepine

Oxcarbazepine caused adverse effects including fatigue, dizziness, and nausea more often than placebo (Appendix Table D149).[201]

Beta Blockers

Atenolol

Treatment discontinuation due to bothersome adverse effects did not differ with atenolol and placebo (low strength of evidence from individual RCTs) (Table 31 and Appendix Table D150).[106, 202, 212] Less than 1 percent of participants discontinued atenolol due to bothersome side effects (Appendix Table D151).[106, 202, 212] Among all examined adverse effects, only rates of slight orthostatic dizziness during the first week of treatments were greater with atenolol than with placebo (Appendix Table D152).

Bisoprolol

Treatment discontinuation due to bothersome adverse effects did not differ with bisoprolol and placebo (low strength of evidence from individual RCTs) (Table 31).[178] In fact, bisoprolol did not cause any adverse effects more often than placebo (Appendix Table D152). A higher dose of bisoprolol did not result in greater rates of adverse effects or treatment discontinuation due to adverse effects.[178] Bisoprolol, 10 mg/day, decreased heart rate when compared to 5 mg/day.[178] Systolic and diastolic blood pressure did not differ with two doses of bisoprolol.[178]

Metoprolol

Treatment discontinuation due to bothersome adverse effects did not differ between metoprolol and placebo (low strength of evidence from individual RCTs) (Table 31).[104] Rates of total adverse effects were greater with metoprolol than with placebo in a single RCT (Appendix Table D152).[103] Metoprolol caused fatigue, tiredness, and gastrointestinal side effects more often than placebo (Appendix Table D152).[103]

Nadolol

Treatment discontinuation due to bothersome adverse effects did not differ between nadolol and placebo (low strength of evidence from individual RCTs) (Table 31).[107] In fact, nadolol did not cause any adverse effects more often than placebo (Appendix Table D152). Increased dose of nadolol did not result in greater rates of adverse effects.[176, 177]

Pindolol

Treatment discontinuation due to bothersome adverse effects did not differ with pindolol and placebo (low strength of evidence from individual RCTs) (Table 31).[109] Patients experienced orthostatic dizziness and faintness more often with pindolol than with placebo (Appendix Table D152).

Antidepressants

Individual underpowered RCTs found no differences in treatment discontinuation due to bothersome adverse effects with placebo and amitriptyline, femoxetine, fluoxetine, or tonabersat (Table 32).

Ergot Alkaloids

In individual underpowered RCTs, treatment discontinuation due to bothersome adverse effects did not differ with placebo, lisuride, or methysergide (Table 33).[213, 214]

Angiotensin Converting Enzyme Inhibitors

Individual RCTs did not examine treatment discontinuation to bothersome adverse effects with lisinopril[119] or captopril.[120] Captopril caused adverse effects no more often than placebo.[120] The rates of any adverse effects were greater than placebo with lisinopril; however, rates of the most common adverse effects with ACE inhibitors (coughing, fatigue, dizziness, or tendency to faint) did not differ between lisinopril and placebo.[119]

Angiotensin II Antagonists

Individual RCTs did not examine treatment discontinuation to bothersome adverse effects with candesartan[121] or telmisartan.[122] Neither drug caused any adverse effect more often than placebo.[121, 122]

Calcium Channel Antagonists

Treatment discontinuation due to bothersome adverse effects did not differ between placebo and nifedipine[215] or between nimodipine[114, 216] and verapamil.[117]

Compared to placebo, verapamil more often caused tolerable constipation that did not result in treatment discontinuation.[117] Nifedipine resulted in adverse effects more often than placebo.[215] Among individual adverse effects, nifedipine increased rates of headache, dizziness, andedema.[215] Nimodipine increased rates of abdominal cramps, but no other examined adverse effects.[115]

NSAID

Individual RCTs found no differences in bothersome adverse effects leading to treatment discontinuation with fenoprofen,[206] naproxen sodium,[217] or tolfenamic acid.[218] Among individual adverse effects, fenoprofen increased rates of fatigue and somnolence.[206]

b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?

The strength of evidence from individual RCTs that examined comparative safety with migraine preventive drugs was low.

Muscle Relaxants

Botulinum Toxin

Comparative safety of botulinum toxin versus topiramate was examined in two RCTs that demonstrated better safety with botulinum toxin than topiramate (Appendix Table D153).[133, 136] Patients experienced depression or mood disturbance, weight loss, paresthesias, or cognitive deficits more often with topiramate (Appendix Table D153).[133, 136]

Comparative safety of botulinum toxin versus divalproex sodium was examined in a single RCT that found a higher risk of ptosis with botulinum toxin (Appendix Table D154).[134] In contrast, risk of fatigue, nausea, and total adverse effects was higher with divalproex (Appendix Table D154).

Comparative safety of botulinum toxin versus amitriptyline was examined in a single RCT that concluded better safety with botulinum toxin (Appendix Table D155).[135] Patients experienced dry mouth, constipation, somnolence, and weight gain several times more often with amitriptyline than with botulinum toxin.[135]

Topiramate

Comparative safety of topiramate was examined in individual RCTs. Topiramate was better tolerated than amitriptyline in adults with migraine (Table 34).[137, 219] Treatment discontinuation due to any adverse effects did not differ between topiramate and zonasamide or valproate (Table 34).

Treatment discontinuation due to exact adverse effects differed with topiramate and other drugs according to individual RCTs (Appendix Table D156). Somnolence and weight gain leading to withdrawal was more common with amitriptyline than topiramate (Appendix Table D156).[137] Treatment discontinuation to treatment failure, however, did not differ between topiramate and amitriptyline or lamotrigine (Appendix Table D157).

Risk of exact adverse effects differed between topiramate and other drugs in individual RCTs (Appendix Table D158). Topiramate increased risk of weight loss when compared to amitriptyline[137] or levetiracetam[141] but not sodium valproate[220] (Appendix Table D158). Topiramate increased risk of paresthesia when compared to amitriptyline,[137, 219] zonasamide,[139] levetiracetam,[141] or sodium valproate[220] (Appendix Table D158). Risk of dry mouth and constipation was lower with topiramate than amitriptyline.[137, 219]

Comparative safety of topiramate combined with amitriptyline versus monotherapy was examined in one small RCT[219] (Appendix Table D159). Treatment discontinuation due to adverse effects did not differ between topiramate combined with amitriptyline and monotherapy (Appendix Table D160). Topiramate combined with amitriptyline increased the risk of adverse effects when compared to amitriptyline alone but not topiramate alone.[219]

Valproate

Valproate Versus Cinnarizine

A single low risk of bias RCT of 125 adults found no differences in adverse effects and treatment discontinuation due to bothersome adverse effects with valproate versus cinnarizine (one RCT of 125 patients, low strength of evidence) (Table 35).[143]

Beta Blockers

Propranolol

Treatment discontinuation due to bothersome adverse effects did not differ with propranolol and aspirin (low strength of evidence from a single RCT of 36 adults) (Appendix Table D140 and Table 29).[221] Evidence of comparative safety with propranolol and nifedipine or divalproex was insufficient due to high risk of bias in individual RCTs (Appendix Table D140).

Treatment discontinuation due to adverse effects did not differ with behavioral migraine management and propranolol (one RCT of 90 adults, low strength of evidence) (Appendix Table D162).[167] Treatment discontinuation due to bothersome adverse effects did not differ with combined behavioral migraine management with propranolol versus propranolol alone (one RCT of 90 adults, low strength of evidence).[167] Combined therapy was more effective than propranolol alone in increasing self-efficacy and internal control over headache (Appendix Table D163).[168]

Off-label Drugs

Off-label Beta Blockers

Metoprolol Versus Clonidine (one RCT of 62 adults, low strength of evidence) (Appendix Table D164)

Metoprolol resulted in treatment discontinuation due to bothersome adverse effects or treatment failure less often than clonidine (Table 36).[159]

Metoprolol Versus Bisoprolol (one RCT of 156 adults, low strength of evidence) (Appendix Table D164)

Treatment discontinuation due to adverse effects did not differ between the two drugs (Table 36)[155] nor did rates of individual examined adverse effects differ between the drugs (Appendix Table D165).

Metoprolol Versus Nebivolol (one RCT of 30 adults, low strength of evidence) (Appendix Table D164)

Treatment discontinuation due to adverse effects did not differ between the two drugs (Table 36).[156] Patients experienced moderate adverse effects, fatigue, and bradicarida more often with metoprolol than with nebivolol (Appendix Table D164). [156]

Metoprolol Versus Aspirin (one RCT of 56 adults, low strength of evidence) (Appendix Table D164)

Gastrointestinal side effects leading to withdrawal were more common with aspirin than metoprolol (Table 36).[157] However, total adverse effects and autonomic nervous system and psychiatric disorders were more common with metoprolol than aspirin (Appendix Table D165).[158]

Metoprolol Versus Clomipramine (one RCT of 126 adults, low strength of evidence) (Appendix Table D164)

Treatment discontinuation because of severe adverse reactions was more common with clomipramine than metoprolol (Table 36).[222] Clomipramine caused insomnia and sweating more often than metoprolol (Appendix Table D1653).[222]

Antidepressants

Clomipramine Versus Metoprolol (one RCT of 126 adults, low strength of evidence)

Clomipramine resulted in greater treatment discontinuation due to bothersome adverse effects than metoprolol (Table 32).[222]

Femoxetine Versus Propranolol (one RCT of 58 adults, low strength of evidence)

Treatment discontinuation due to bothersome adverse effects did not differ between femoxetine and propranolol (Table 32).[153]

Amitriptyline Versus Spinal Manipulation (one RCT of 147 adults, low strength of evidence) (Table 37)[165]

Treatment discontinuation due to adverse effects occurred less with spinal stimulation than with amitriptyline.[165] Strength of evidence was low due to risk of bias and imprecise estimate (Appendix Table D166).[165]

Treatment discontinuation due to adverse effects did not differ between combined treatment using spinal manipulation with amitriptyline and amitriptyline alone (Appendix Table D167).[165]

Ergot Alkaloids

A single RCT of 253 adults (low strength of evidence) found that treatment discontinuation due to adverse effects was lower with lisuride than with methysergide (Table 33).[205]

Indirect Evidence of Comparative Safety of Drugs for Migraine Prevention in Adults

Indirect Bayesian network meta-analyses demonstrated that topiramate, divalproex, off-label antiepileptics, antidepressants, and ergot alkaloids resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Appendix Table D168). Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Bothersome adverse effects leading to treatment discontinuation were examined with 28 different drugs from eight drug classes. We analyzed comparative effectiveness of 10 treatments including placebo, topiramate, valproate, divalproex, propranolol, off-label beta blockers, off-label antidepressants, off-label antiepileptics, and other off-label drugs (ergot alkaloids or dopaminergic agents). Topiramate, divalproex, off-label antiepileptics (acetazolamide, carbamazepin, gabapentin, lamotrigen, levetiracetam, oxcarbazepine), antidepressants, and other off-label drugs (ergot alkaloids or dopaminergic agents) resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Appendix Table D168). Divalproex and off-label antiepileptics resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers. Divalproex and off-label antiepileptics led to the highest rates of treatment discontinuation due to bothersome adverse effects.

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

We found no studies that examined adverse effects with different approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring).

Table 22. Adverse effect with botulinum toxin vs. placebo for migraine prevention in adults (magnitude of the effect and strength of evidence from randomized controlled clinical trials)

Adverse effect	Sample, References	Rate, percent with botulinum toxin [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Any adverse effect	5031[78, 82, 169, 170, 223-227]	47.5 [29.4]	6 (5 to 11)	155 (90 to 220)	Moderate
Back pain	1112[77, 170, 227]	2.2 [0.5]	59 (32 to 333)	17 (3 to 31)	High
Discontinuations related to adverse effect	1384[225, 226]	3.8 [1.1]	38 (23 to 100)	26 (10 to 43)	Moderate
Dizziness	893[77, 78, 81, 227]	1.7 [0.9]			Moderate
Dysphagia	1057[78, 170]	3.3 [0.3]	36 (23 to 83)	28 (12 to 44)	High
Eyelid edema	915[81, 169, 227]	3.6 [0.3]			High
Headache	2204[78, 81, 169, 170, 223, 227]	5.2 [4.5]			High
Hypertonia	1426[78, 170, 227]	7.1 [1.3]	16 (12 to 24)	62 (42 to 82)	High
Neck pain	2233[78, 81, 225, 227]	14.1 [1.4]	9 (6 to 17)	111 (58 to 164)	Moderate
Neck rigidity	1467[77, 78, 170, 227]	9.2 [1.8]	13 (9 to 24)	75 (41 to 110)	Moderate
Pain	2319[77, 78, 81, 170, 227]	3.6 [2.1]			Moderate
Blepharoptosis	2454[76, 78, 81, 169, 170, 223, 224, 227]	6.4 [0.8]	20 (14 to 34)	49 (29 to 69)	High
Muscle weakness	1968[78, 170, 223, 225]	15.8 [0.1]	8 (5 to 18)	132 (56 to 209)	Moderate
Fever	587[77, 81, 169]	5.3 [7.1]			Moderate

CI – confidence interval

Table 23. Adverse effects with botulinum toxin vs. placebo meta-regression by study level factors (log of relative risk in randomized controlled clinical trials)

Contributing factor	Adverse effect	Contributing variable	Meta-regression coefficient	Lower 95% CI	Upper 95% CI
Drug	Blepharoptosis	Dose	0.00	-0.01	0.01
Patient	Blepharoptosis	Age	0.22	-0.30	0.74
Patient	Blepharoptosis	Years of migraine	-0.05	-0.11	0.01
Study	Blepharoptosis	percent women	-0.02	-0.15	0.11
Study	Blepharoptosis	Control rate	0.99	-102.24	104.22
Study	Blepharoptosis	Loss of followup	-0.04	-0.10	0.03
Study	Blepharoptosis	Risk of bias	-0.56	-1.79	0.67
Drug	Adverse effects	Dose	0.00	0.00	0.01
Patient	Adverse effects	Age	0.04	-0.12	0.20
Patient	Adverse effects	Years of migraine	-0.05	-0.11	0.01
Study	Adverse effects	percent women	-0.02	-0.15	0.11
Study	**Adverse effects**	**Control rate**	**-1.92**	**-2.46**	**-1.37**
Study	Adverse effects	Loss of followup	0.02	0.00	0.04
Study	Adverse effects	Risk of bias	0.06	-0.34	0.47
Drug	Headache	Dose	0.00	0.00	0.01
Patient	Headache	Age	0.25	-0.16	0.67
Patient	Headache	Years of migraine	0.01	-0.10	0.11
Study	Headache	percent women	-0.08	-0.25	0.08
Study	Headache	Control rate	8.52	-34.54	51.59
Study	Headache	Loss of followup	0.01	-0.03	0.06
Study	Headache	Risk of bias	-0.11	-1.24	1.02

Bold –significant differences at 95% confidence limit
CI – confidence interval

Table 24. Treatment discontinuation due to adverse effects with topiramate in adults

Definition of the outcome	Daily dose	Sample References	Conclusion	Strength of evidence
Discontinued due to adverse events	100 mg/day	1719[86, 87, 189, 190, 228-230]	Topiramate, 100 mg/day, resulted in treatment discontinuation due to adverse effects more often than placebo	Moderate
Discontinued due to adverse events	200 mg/day	586[84, 87, 192, 231]	Topiramate, 200 mg/day, resulted in treatment discontinuation due to adverse effects more often than placebo	Low
Discontinuations due to adverse events	50 mg/day	310[87, 231]	Topiramate, 50 mg/day, did not result in treatment discontinuation due to adverse effects more often than placebo	Low
Discontinued due to lack of efficacy	100 mg/day	1669[86, 87, 189, 190, 228, 229]	Topiramate, 100 mg/day, did not result in treatment discontinuation due to treatment failure more often than placebo	Moderate
Discontinued due to lack of efficacy	Any dose	592[84, 87, 190, 192]	Topiramate, 100 mg/day, did not result in treatment discontinuation due to treatment failure more often than placebo	Low
Discontinued due to lack of efficacy	50 mg/day	319[87, 190]	Topiramate, 200 mg/day, did not result in treatment discontinuation due to treatment failure more often than placebo	Low
Dizziness leading to withdrawal	50-200 mg/day	1867[27, 210, 230]	Topiramate, 50-200 mg/day, did not result in treatment discontinuation due to dizziness more often than placebo	Moderate
Fatigue leading to withdrawal	50-200 mg/day	1982[27, 189, 210, 230]	Topiramate, 50-200 mg/day, resulted in treatment discontinuation due to fatigue more often than placebo	High
Insomnia leading to withdrawal	50-200 mg/day	1867[27, 210, 230]	Topiramate, 50-200 mg/day, resulted in treatment discontinuation due to insomnia more often than placebo	Moderate
Language problems leading to withdrawal	50-200 mg/day	1630[210 230]	Topiramate, 50-200 mg/day, resulted in treatment discontinuation due to language problems more often than placebo	Moderate
Paresthesia leading to withdrawal	50-200 mg/day	1982[27, 189, 210, 230]	Topiramate, 50-200 mg/day, resulted in treatment discontinuation due to paresthesia more often than placebo	Moderate
Somnolence leading to withdrawal	50-200 mg/day	1695[189, 210]	Topiramate, 50-200 mg/day, did not result in treatment discontinuation due to somnolence more often than placebo	Moderate
Taste perversion leading to withdrawal	50-200 mg/day	1745[189, 210, 230]	Topiramate, 50-200 mg/day, resulted in treatment discontinuation due to taste perversion more often than placebo	Moderate
Early discontinuation	50-200 mg/day	3264[84, 86, 88, 189, 192, 210, 228, 229]	Topiramate, 50-200 mg/day, did not result in treatment discontinuation more often than placebo	Low
Difficulty with concentration/ attention leading to withdrawal	50-200 mg/day	2367[27, 189, 210, 229, 230]	Topiramate, 50-200mg/day, resulted in treatment discontinuation due cognitive symptoms more often than placebo	High
Early discontinuation due to adverse effects	100 vs. 50 mg/day	621[210]	Increase in dose of topiramate from 50 to 100 mg/day resulted in greater rates of treatment discontinuation due to adverse effects	Low
Early discontinuation due to adverse effects	200 vs. 50 or 100 mg/day	490[87, 190]	Increase in dose of topiramate to 200 mg/day did not result in greater rates of treatment discontinuation due to adverse effects when compared to 50 or 100 mg/day	Low

Table 25. Discontinuation due to adverse effects with topiramate in randomized controlled clinical trials of migraine prevention in adults

Outcome	Daily dose of topiramate	Sample, Reference	Rate, percent with drug [placebo]	Relative risk (95% CI)	Adjusted risk difference (95% CI)	Bayesian odds ratio (2.5 to 97.5%)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Discontinued due to adverse events	**100 mg/day**	**1719[86, 87, 189, 190, 228-230]**	**12.6 [6.2]**	**1.6 (1.1 to 2.2)**	**0.04 (0.01 to 0.06)**	**1.9 (1.2 to 3.0)**	**28 (17 to 71)**	**36 (14 to 58)**	**Moderate**
Discontinued due to adverse events	**200 mg/day**	**586[84, 87, 192, 231]**	**22.2 [6.6]**	**2.6 (1.5 to 4.6)**	**0.15 (0.07 to 0.22)**	**3.9 (1.9 to 8.8)**	**7 (4 to 15)**	**146 (68 to 223)**	**Low**
Discontinuations due to adverse events	50 mg/day	310[87, 231]	17.5 [10.8]	1.5 (0.7 to 2.9)	0.06 (-0.03 to 0.15)	1.9 (0.7 to 5.5)	17 (7 to -34)	58 (-29 to 145)	Low
Dizziness leading to withdrawal	50-200 mg/day	1867[27, 210, 230]	2.0 [1.8]	1.2 (0.6 to 2.5)	0.00 (-0.01 to 0.02)	1.0 (0.4 to 2.4)			Moderate
Fatigue leading to withdrawal	**50-200 mg/day**	**1982[27, 189, 210, 230]**	**4.1 [1.0]**	**3.3 (1.4 to 7.7)**	**0.03 (0.01 to 0.04)**	**3.9 (1.6 to 10.6)**	**38 (23 to 125)**	**26 (8 to 43)**	**High**
Insomnia leading to withdrawal	**50-200 mg/day**	**1867[27, 210, 230]**	**2.6 [1.2]**	**2.4 (1.1 to 5.2)**	**0.02 (0.00 to 0.03)**	**2.3 (0.9 to 6.2)**	**63 (34 to 250)**	**16 (4 to 29)**	**Moderate**
Language problems leading to withdrawal	**50-200 mg/day**	**1630[210, 230]**	**1.9 [0.4]**	**3.2 (1.0 to 10.6)**	**0.01 (0.00 to 0.02)**	**5.5 (1.4 to 41.1)**	**71 (42 to 333)**	**14 (3 to 24)**	**Moderate**
Paresthesia leading to withdrawal	**50-200 mg/day**	**1982[27, 189, 210, 230]**	**6.9 [0.7]**	**8.6 (3.8 to 19.7)**	**0.06 (0.04 to 0.09)**	**12.4 (4.9 to 37.4)**	**17 (12 to 29)**	**60 (35 to 85)**	**Moderate**
Somnolence leading to withdrawal	50-200 mg/day	1695[189, 210]	1.8 [1.8]	0.9 (0.4 to 1.9)	0.00 (-0.02 to 0.01)	1.0 (0.4 to 2.6)			Moderate
Taste perversion leading to withdrawal	**50-200 mg/day**	**1745[189, 210, 230]**	**1.1 [0.0]**	**3.0 (0.8 to 11.7)**	**0.01 (0.00 to 0.02)**		**100 (56 to 500)**	**10 (2 to 18)**	**Moderate**
Early discontinuation	50-200 mg/day	3264[84, 86, 88, 189, 192, 210, 228, 229]	37.6 [32.2]	1.1 (0.9 to 1.3)	0.03 (-0.03 to 0.08)	1.1 (0.9 to 1.5)			Low
Difficulty with concentration/attention leading to withdrawal	**50-200 mg/day**	**2367[27, 189, 210, 229, 230]**	**4.9 [1.3]**	**3.5 (1.7 to 7.3)**	**0.04 (0.01 to 0.06)**	**4.1 (1.5 to 9.8)**	**28 (16 to 100)**	**36 (10 to 63)**	**High**

Bold – significant at 95% confidence limit
CI – confidence interval

Table 26. Adverse effects with topiramate in adults with migraine, significant results from pooled analysis of randomized controlled clinical trials

Outcome	Sample, reference	Rate percent with drug [placebo]	Number needed to treat to harm 1 patient (95% CI)	Attributable events per 1000 treated (95% CI)
Any adverse event	3079[84, 86, 88, 187, 210, 229]	77.7 [57.7]	8 (5 to 16)	129 (61 to 196)
Anorexia	3390[84, 86, 88, 186, 210, 228-230, 232]	11.2 [4.9]	19 (12 to 43)	54 (23 to 85)
Anxiety	1620[210, 232]	5.4 [2.6]	34 (21 to 111)	29 (9 to 48)
Paresthesia	3342[84-86, 88, 189, 192, 210, 228-230]	41.1 [9.6]	3 (3 to 5)	303 (218 to 388)
Difficulty with concentration	2531[86, 88, 210, 228, 230]	7.0 [3.2]	28 (16 to 111)	36 (9 to 64)
Diarrhea	2035[192, 210, 229]	9.9 [3.8]	18 (13 to 29)	57 (34 to 80)
Fatigue	3572[84, 86, 88, 187, 189, 210, 228-230]	14.2 [8.2]	22 (15 to 40)	45 (25 to 66)
Hypoesthesia	2621[187, 210, 228, 229]	7.5 [1.3]	17 (13 to 24)	60 (42 to 78)
Cognitive symptoms	2415[84, 88, 189, 192, 210, 228, 230]	8.9 [3.2]	18 (13 to 32)	56 (31 to 80)
Nausea	3079[84, 86, 88, 210, 228, 229]	11.1 [6.9]	30 (18 to 125)	33 (8 to 57)
Somnolence	3058[84, 88, 187, 189, 210, 228-230]	7.5 [4.8]	45 (24 to 500)	22 (2 to 41)
Alteration of taste	120[192, 230]	32.8 [1.8]	3 (2 to 5)	313 (191 to 435)
Abnormal vision	1620[210, 232]	5.7 [2.4]	32 (17 to 250)	31 (4 to 59)
Weight loss	2512[84, 86, 189, 210, 230, 232]	10.6 [3.7]	13 (9 to 25)	77 (40 to 115)

CI – confidence interval

Table 27. Treatment discontinuation due to bothersome adverse effects and adverse effects with divalproex vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials

Outcome	Daily dose	Reference	Sample	Rate, percent with divalproex [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Discontinuations due to intolerance	Mean average dose 1087 mg/d	Mathew, 1995[91]	107	12.9 [5.4]	NS	NS	
Discontinuations due to intolerance	Mean average dose 871 mg/d	Freitag, 2002[90]	239	8.1 [8.6]	NS	NS	
Discontinuations due to intolerance	Pooled		346	9.8 [7.8]	NS	NS	Low
Abdominal pain	Mean average dose 871 mg/d	Freitag, 2002[90]	239	6.5 [5.2]	NS	NS	Low
Alopecia	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**12.9 [0.0]**	**8 (5 to 24)**	**129 (41 to 216)**	**Low**
Any	Mean average dose 871 mg/d	Freitag, 2002[90]	239	67.5 [69.8]	NS	NS	Low
Asthenia	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**31.4 [8.1]**	**4 (3 to 11)**	**233 (93 to 373)**	**Low**
Asthenia	500 mg	Klapper, 1997[92]	60	8.9 [9.1]	NS	NS	Low
Asthenia	1000 mg	Klapper, 1997[92]	57	9.3 [9.1]	NS	NS	Low
Asthenia	1500 mg	Klapper, 1997[92]	58	22.7 [9.3]	NS	NS	Low
Asthenia	Mean average dose 871 mg/d	Freitag, 2002[90]	239	7.3 [10.3]	NS	NS	Low
Back pain	500 mg	Klapper, 1997[92]	60	6.7 [9.1]	NS	NS	Low
Back pain	1000 mg	Klapper, 1997[92]	57	4.7 [9.1]	NS	NS	Low
Back pain	1500 mg	Klapper, 1997[92]	58	13.6 [9.3]	NS	NS	Low
Diarrhea	500 mg	Klapper, 1997[92]	60	6.7 [4.5]	NS	NS	Low
Diarrhea	1000 mg	Klapper, 1997[92]	58	4.7 [4.5]	NS	NS	Low
Diarrhea	1500 mg	Klapper, 1997[92]	59	18.2 [4.6]	NS	NS	Low
Diarrhea	Mean average dose 871 mg/d	Freitag, 2002[90]	239	7.3 [3.4]	NS	NS	Low
Dizziness	500 mg	Klapper, 1997[92]	60	6.7 [4.5]	NS	NS	Low
Dizziness	1000 mg	Klapper, 1997[92]	58	7.0 [4.5]	NS	NS	Low
Dizziness	1500 mg	Klapper, 1997[92]	59	20.5 [4.6]	NS	NS	Low
Dyspepsia	500 mg	Klapper, 1997[92]	60	6.7 [9.1]	NS	NS	Low
Dyspepsia	1000 mg	Klapper, 1997[92]	57	18.6 [9.1]	NS	NS	Low
Dyspepsia	1500 mg	Klapper, 1997[92]	58	15.9 [9.3]	NS	NS	Low
Dyspepsia	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	6.5 [4.3]	NS	NS	Low
Flu syndrome	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	8.1 [8.6]	NS	NS	Low
Infection	500 mg	Klapper, 1997[92]	60	17.8 [18.2]	NS	NS	Low
Infection	1000 mg	Klapper, 1997[92]	58	16.3 [18.2]	NS	NS	Low
Infection	1500 mg	Klapper, 1997[92]	59	20.5 [18.6]	NS	NS	Low
Infection	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	14.6 [13.8]	NS	NS	Low

Table 27. Treatment discontinuation due to bothersome adverse effects and adverse effects with divalproex vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials (continued)

Outcome	Daily dose	Reference	Sample	Rate, percent with divalproex [placebo]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Nausea	**Mean average dose of divalproex sodium was 1087 mg/d**	**Mathew, 1995[91]**	**107**	**45.7 [13.5]**	**3 (2 to 6)**	322 (162 to 482)	**Low**
Nausea	**500 mg**	**Klapper, 1997[92]**	**60**	**26.7 [6.8]**	**5 (3 to 52)**	200 (19 to 381)	**Low**
Nausea	1000 mg	Klapper, 1997[92]	57	9.3 [6.8]	NS	NS	Low
Nausea	**1500 mg**	**Klapper, 1997[92]**	**59**	**34.1 [7.0]**	**4 (2 to 12)**	274 (86 to 463)	**Low**
Nausea	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	14.6 [8.6]	NS	NS	Low
Pain	500 mg	Klapper, 1997[92]	60	8.9 [6.8]	NS	NS	Low
Pain	1000 mg	Klapper, 1997[92]	57	7.0 [6.8]	NS	NS	Low
Pain	1500 mg	Klapper, 1997[92]	59	11.4 [7.0]	NS	NS	Low
Sinusitis	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	3.3 [7.8]	NS	NS	Low
Somnolence	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**30.0 [5.4]**	**4 (3 to 9)**	246 (116 to 376)	**Low**
Somnolence	500 mg	Klapper, 1997[92]	60	6.7 [4.5]	NS	NS	Low
Somnolence	1000 mg	Klapper, 1997[92]	58	7.0 [4.5]	NS	NS	Low
Somnolence	1500 mg	Klapper, 1997[92]	59	18.2 [4.6]	NS	NS	Low
Somnolence	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	6.5 [1.7]	NS	NS	Low
Tremor	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**12.9 [0.0]**	**8 (5 to 24)**	129 (41 to 216)	**Low**
Tremor	500 mg	Klapper, 1997[92]	60	0.0 [0.0]	NS	NS	Low
Tremor	1000 mg	Klapper, 1997[92]	57	7.0 [0.0]	NS	NS	Low
Tremor	**1500 mg**	**Mathew, 1995[91]**	**59**	**15.9 [0.0]**	**6 (3 to 48)**	159 (21 to 297)	**Low**
Vomiting	**Mean average dose 1087 mg/d**	**Mathew, 1995[91]**	**107**	**18.6 [0.0]**	**5 (4 to 11)**	186 (88 to 284)	**Low**
Vomiting	500 mg	Klapper, 1997[92]	60	4.4 [2.3]	NS	NS	Low
Vomiting	1000 mg	Klapper, 1997[92]	57	4.7 [2.3]	NS	NS	Low
Vomiting	1500 mg	Klapper, 1997[92]	58	11.4 [2.3]	NS	NS	Low
Vomiting	Mean average dose of study: 871 mg/d	Freitag, 2002[90]	239	6.5 [1.7]	NS	NS	Low

Bold – significant difference at 95% confidence limit
CI – confidence interval
NS – not significant

Table 28. Treatment discontinuation due to bothersome adverse effects with valproate vs. placebo for migraine prevention in adults, results from moderate risk of bias randomized controlled clinical trial

Adverse effect that lead to treatment discontinuation	Daily dose	Reference	Sample	Rate, percent with valproate [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Strength of evidence
Discontinuations due to adverse effects	400 mg twice a day	Hering, 1992[94]	64	3.1 [6.3]	0.5 (0.0 to 5.2)	-0.03 (-0.13 to 0.07)	Low

CI – confidence interval

Table 29. Treatment discontinuation due to adverse effects with propranolol or timolol for migraine prevention in adults, results from randomized controlled clinical trials

	Active treatment	Control treatment	Reference	Sample	Rate with active treatment, percent	Rate with control treatment, percent	Number needed to treat (95% CI)	Attributable events (95% CI)	Strength of evidence
Treatment discontinuation due to adverse	Propranolol	Placebo	Diamond, 1976[194]	166	7.2	1.2			Low
Treatment discontinuation due to adverse	Divalproex	Propranolol	Kaniecki, 1997[144]	74	10.8	2.7			Insufficient
Treatment discontinuation due to adverse	**Propranolol**	**Nifedipine**	**Albers, 1989[150]**	**40**	**25.0**	**65.0**	**-3 (-8 to -1)**	**-400 (-682 to -118)**	**Insufficient**
Treatment discontinuation due to adverse	Propranolol	Acetylsalicylic acid	Baldrati, 1983[221]	36	11.1	16.7			Low
Treatment discontinuation due to adverse	Propranolol	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[166]	89	2.3-6.3	8.9-18.4			Insufficient
Treatment discontinuation due to adverse	**Propranolol + Amitriptyline**	**Abortive treatment with ergotamine and analgesics (control)**	**Mathew, 1981[166]**	**96**	**4.3**	**18.4**	**-7 (-55 to -4)**	**-141 (-264 to -18)**	**Insufficient**
Moderate chest pain on day 28 leading to discontinuation	Timolol	Placebo	Stellar, 1984[101]	94	2.1	**0**	Not significant	Not significant	Low
Discontinued therapy because of severe epigastric distress and fecal impaction	Timolol	Placebo	Stellar, 1984[101]	94	2.1	**0**	Not significant	Not significant	Low
Withdrew due to adverse experiences	Timolol	Placebo	Stellar, 1984[101]	94	4.3	**0**	Not significant	Not significant	Low

Bold – significant at 95% confidence limit
CI – Confidence interval

Table 30. Treatment discontinuation due to bothersome adverse effects with off label antiepileptic drugs vs. placebo for migraine prevention in adults, results from randomized controlled clinical trials (low strength of evidence)

Active drug, daily dose	Reference Risk of bias	Sample	Events/ randomized with active drug	Events/ randomized with placebo	Rate, percent with active drug [placebo]	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)
Acetazolamide 500 mg (250 twice daily)	**Vahedi, 2002[197] Risk of bias Low**	**53**	**9/26**	**2/27**	**34.6 [7.4]**	**4.7 (1.1 to 19.6)**	**0.27 (0.06 to 0.48)**	**4 (2 to 16)**	**272 (64 to 480)**
Carbamazepine One tablet 3 times a day	Rompel, 1970[198] Risk of bias Moderate	96	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)	NS	NS
Gabapentin Titrated up to 2400 mg daily	Mathew, 2001[199] Risk of bias Moderate	143	16/98	4/45	16.3 [8.9]	1.8 (0.7 to 5.2)	0.07 (-0.04 to 0.19)	NS	NS
Gabapentin 900 mg (300 x 3)	Wessely, 1987[200] Risk of bias Low	45	2/23	1/22	8.7 [4.5]	1.9 (0.2 to 19.6)	0.04 (-0.10 to 0.19)	NS	NS
Lamotrigine 25 mg/day for 2 weeks, 50 mg/day for 2 weeks, then 200 mg/day	**Steiner, 1997[211] Risk of bias Low**	**58**	**7/18**	**3/40**	**38.9 [7.5]**	**5.2 (1.5 to 17.8)**	**0.31 (0.07 to 0.55)**	**3 (2 to 13)**	**314 (74 to 553)**
Lamotrigine 25mg BD	Gupta, 2007[138] Risk of bias Low	120	3/60	3/60	5.0 [5.0]	1.0 (0.2 to 4.8)	0.00 (-0.08 to 0.08)	NS	NS
Oxcarbazepine Maximum tolerated dose of 1,200 mg/day	Silberstein, 2008[201] Risk of bias Low	170	8/85	4/85	9.4 [4.7]	2.0 (0.6 to 6.4)	0.05 (-0.03 to 0.12)	NS	NS

NS – not significant
Bold – significant at 95% confidence limit
CI – confidence level

Table 31. Treatment discontinuation due to adverse effects with beta blockers for migraine prevention in adults, evidence from randomized controlled clinical trials

Definition of the outcome	Drug name	Reference	Sample	Rate of outcome, percent with drug [placebo]	Number needed to treat to harm 1 patient	Attributable events per 1000 treated	Strength of evidence
Withdrawal due to side effects	Atenolol	Johannsson, 1987[212]	144	0.0 [4.2]	Not significant	Not significant	Low
Withdrawal due to mood alternations and increased tiredness	Atenolol	Forssman, 1982-83 [106, 202]	48	4.2 [0.0]	Not significant	Not significant	Low
Withdrawal due to intolerable increase of headache attack	Atenolol	Forssman, 1982-83 [106, 202]	48	0.0 [4.2]	Not significant	Not significant	Low
Dropped out of the study due to adverse effects	Bisoprolol	van de Ven, 1997[178]	111	5.4 [5.3]	Not significant	Not significant	Low
Discontinued due to side-effects	Metoprolol	Andersson, 1983[104]	71	2.9 [2.7]	Not significant	Not significant	Low
Discontinued due to bradycardia	Nadolol	Freitag, 1984[107]	32	4.2 [0.0]	Not significant	Not significant	Low
Discontinued due to side-effects	Pindolol (LB-46)	Sjaastad, 1972[109]	56	10.7 [0.0]	Not significant	Not significant	Low

Table 32. Treatment discontinuation due to adverse effects with antidepressants, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates

Outcome	Active drug, Daily dose	Control drug	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)
Amitriptyline 50 mg to 100 mg	Placebo	Couch, 1979[204] Risk of bias Moderate	5/55	2/61	9.1 [3.3]	2.8 (0.6 to 13.7)	0.06 (-0.03 to 0.15)		
Amitriptyline 25-100 mg	Placebo	Couch, 2011[233] Risk of bias Moderate	23/194	13/197	11.9 [6.6]	1.8 (0.9 to 3.4)	0.05 (0.00 to 0.11)		
Clomipramine 100 mg/day	**Metoprolol 100mg/day**	**Langohr, 1985[222] Risk of bias** Moderate	**18/63**	**0/63**	**28.6 [0.0]**	**37.0 (2.3 to 600.9)**	**0.29 (0.17 to 0.40)**	**3 (3 to 6)**	**286 (173 to 399)**
Femoxetine 200 mg daily increasing to a standard dosage of 600 mg daily	Placebo	Orholm, 1986[234] Risk of bias Moderate	4/31	2/34	12.9 [5.9]	2.2 (0.4 to 11.2)	0.07 (-0.07 to 0.21)		
Fluoxetine, 40 mg	Placebo	Steiner, 1998[235] Risk of bias High	4/27	4/26	14.8 [15.4]	1.0 (0.3 to 3.5)	-0.01 (-0.20 to 0.19)		
Tonabersat 20 mg -40 mg	Placebo	Goadsby, 2009[112] Risk of bias Low	2/59	1/65	3.4 [1.5]	2.2 (0.2 to 23.7)	0.02 (-0.04 to 0.07)		
Femoxetine 200 mg daily 1st week and 400 mg daily after	Propranolol 80 mg daily for 1st week and 160 mg daily later	Kangasniemi, 1983[153] Risk of bias Moderate	3/29	0/29	10.3 [0.0]	7.0 (0.4 to 129.7)	0.10 (-0.02 to 0.23)		

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 33. Treatment discontinuation due to adverse effects with ergot alkaloids, results from randomized controlled clinical trials, strength of evidence is low due to risk of bias and imprecision of the estimates

Outcome	Active drug, Daily dose	Reference Risk of bias	Events/ randomized with active drug	Events/ randomized with control drug	Rate, percent with active [control] drug	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI))
Lisuride 0.025 mg three times a day	Placebo	Somerville, 1976[213] Risk of bias Moderate	12/75	5/75	16.0 [6.7]	2.4 (0.9 to 6.5)	0.09 (-0.01 to 0.19)		
Methysergide 1 mg q.d.s.	Placebo	Whewell, 1966[214] Risk of bias Moderate	1/74	2/74	1.4 [2.7]	0.5 (0.0 to 5.4)	-0.01 (-0.06 to 0.03)		
Lisuride 25 mcg tid	**Methysergide 2 mg tid**	**Hermann, 1977[205] Risk of bias** Moderate	**22/130**	**48/123**	**16.9 [39.0]**	**0.4 (0.3 to 0.7)**	**-0.22 (-0.33 to -0.11)**	**-5 (-9 to -3)**	**-221 (-329 to -113)**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 34. Treatment discontinuation due to any adverse effects with topiramate vs. other drugs for migraine prevention in adults

Adverse effects leading to withdrawal	Active	Control	Reference	Sample	Rate, percent with topiramate [control drug]	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Aggravation of migraine leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	0.0 [1.8]	NS	NS	Low
Anxiety leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	1.7 [0.0]	NS	NS	Low
Confusion leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	1.7 [0.0]	NS	NS	Low
Dizziness leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	1.7 [0.0]	NS	NS	Low
Dry mouth leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	0.0 [1.8]	NS	NS	Low
Fatigue leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	3.4 [2.4]	NS	NS	Low
Hypoesthesia leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[137]	347	1.7 [0.0]			Low
Somnolence leading to withdrawal	**Topiramate**	**Amitriptyline**	**Dodick, 2009[137]**	**347**	**0.0 [4.1]**	**-24 (-104 to -14)**	**-41 (-73 to -10)**	**Low**
Weight increase leading to withdrawal	**Topiramate**	**Amitriptyline**	**Dodick, 2009[137]**	**347**	**0.0 [4.7]**	**-21 (-73 to -12)**	**-47 -81 to -14)**	**Low**
Withdrew due to drowsiness	Topiramate	Valproate (slow-release)	Bartolini, 2005[140]	44	9.1 [13.6]	NS	NS	Low
Left the study due to impaired concentration	Topiramate	Zonasamide	Mohammadiani nejad, 2011[139]	80	0.0 [2.5]	NS	NS	Low
Left the study due to intolerable paresthesia	Topiramate	Zonasamide	Mohammadiani nejad, 2011[139]	80	5.0 [0.0]	NS	NS	Low
Left the study due to unbearable restless leg syndrome	Topiramate	Zonasamide	Mohammadiani nejad, 2011[139]	80	0.0 [2.5]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 100mg	Amitriptyline 100mg	Dodick, 2009[137]	347	19.7 [22.5]	NS	NS	Low
Discontinued due to adverse effects	Topiramate + Amitriptyline amitriptyline	Amitriptyline	Keskinbora, 2008[219]	51	4.3 [14.3]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 200mg	Amitriptyline 150mg	Keskinbora, 2008[219]	52	8.3 [14.3]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 200mg)	Topiramate + Amitriptyline	Keskinbora, 2008[219]	47	8.3 [4.3]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[138]	120	5.0 [5.0]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[141]	28	7.7 [0.0]	NS	NS	Low

Bold – significant at 95% confidence limit
CI – confidence interval
NS – not significant

Table 35. Treatment discontinuation due to bothersome adverse effects with valproate (600 mg/day) vs. cinnarizine (75 mg/day), low strength of evidence from low risk of bias randomized controlled clinical trial[143]

Definition outcomes	Events/randomized with valproate	Events/randomized with cinnarizine	Rate, percent with valproate [cinnarizine]	Relative risk (95% CI)	Absolute risk difference (95% CI)
Adverse effects of treatment	13/67	13/58	19.4 [22.4]	0.9 (0.4 to 1.7)	-0.03 (-0.17 to 0.11)
Discontinuations due to adverse effects	3/67	2/58	4.5 [3.4]	1.3 (0.2 to 7.5)	0.01 (-0.06 to 0.08)

CI – confidence interval

Table 36. Comparative safety of beta blockers for migraine prevention in adults, treatment discontinuation due to bothersome adverse effects in randomized controlled clinical trials

Definition of the outcome	Reference	Active drug	Control drug	Sample	Rate of outcome in active group [Rate of outcome in control group], percent	Number needed to treat to harm one patient (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Withdrew because of side effects and/or lack of efficacy	**Louis, 1985[159]**	**Metoprolol**	**Clonidine**	**62**	**0.0 [12.9]**	**-8 (-870 to -4)**	**-129 (-257 to -1)**	**Low**
Discontinued due to side-effects	Worz, 1991[155]	Metoprolol	Bisoprolol	156	6.4 [10.3]	Not significant	Not significant	Low
Patient withdrawal due to events	Schellenberg, 2008[156]	Metoprolol	Nebivolol	30	7. [6.3]	Not significant	Not significant	Low
Drowsiness leading to withdrawal	Grotemeyer, 1990[157]	Metoprolol	Acetylsalicylic acid	56	7.1 [0.0]	Not significant	Not significant	Low
Gastrointestinal side-effects leading to withdrawal	**Grotemeyer, 1990[157]**	**Metoprolol**	**Acetylsalicylic acid**	**56**	**0.0 [17.9]**	**-6 (-35 to -3)**	**-179 (-329 to -28)**	**Low**
Discontinued treatment because of severe adverse reactions	**Langohr, 1985[222]**	**Clomipramine**	**Metoprolol**	**126**	**28.6 [0.0]**	**3 (3 to 6)**	**286 (173 to 399)**	**Low**

Bold – significant differences at 95% confidence limit
CI – confidence interval

Table 37. Treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual moderate risk of bias randomized controlled clinical trial[165]

Definition of the outcome	Active treatment	Control treatment	Sample	Rate with active, percent [control] treatments	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Withdrawn due to side-effects	**Spinal Manipulation**	**Amitriptyline 100mg/day**	**147**	**0.0 [10.0]**	**-10 (-38 to -6)**	**-100 (-174 to -26)**	**Low**
Withdrawn due to side effects	Spinal Manipulation + Amitriptyline 100 mg/day	Amitriptyline 100 mg/days	141	5.6 [10.0]	Not significant	Not significant	Low
Withdrawn due to side effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100 mg/day	148	0.0 [5.6]	Not significant	Not significant	Low

Bold – significant differences at 95% confidence limit
CI – confidence interval

Question 3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?

Muscle Relaxants

Botulinum Toxin

Placebo Responders

Efficacy of botulinum toxin among placebo responders versus nonresponders was examined in four RCTs.[78, 227, 236, 237] Botulinum toxin was better than placebo in preventing migraine attacks/month by ≥50 percent, irrespective of placebo response according to the BOTULINUM TOXIN CDH Study Group.[78] Magnitude of the effect was slightly larger in placebo nonresponders (RR 2.2, 95 percent CI, 1.4 to 3.4) than in placebo responders (RR 1.6, 95 percent CI, 1.1 to 2.4).[78] The European BoNTA Headache Study Group demonstrated no additional benefits from increasing botulinum toxin dose, regardless of placebo response.[237] The number of migraine days did not differ by dose (75, 15, or 225U) of botulinum toxin.[237]

Baseline Migraine Frequency

Botulinum toxin was more effective in patients with a higher mean baseline migraine frequency in a single RCT from the BOTULINUM TOXIN North American Episodic Migraine Study Group.[227] Botulinum toxin decreased the likelihood of use of drugs for acute attacks in patients with more than 12 migraine days per month at baseline (RR 0.78, 95 percent CI, 0.66 to 0.92).[227]

Concurrent Prophylactic Medication Use

Botulinum toxin caused adverse effects more often than placebo (blepharoptosis, muscle weakness, and neck pain, irrespective of concurrent prophylactic medication use) according to the BOTULINUM TOXIN CDH Study Group.[236]

Antiepileptics

Topiramate

Sex

Topiramate caused a complete cessation of migraine attacks and a reduction of monthly migraine attacks by 50 percent in women but not men according to one low risk of bias RCT.[186] Topiramate caused a complete cessation of migraine attacks in 37 (95 percent CI, 8 to 67) and a reduction of monthly migraine attacks by 50 percent in 249 (95 percent CI, 178 to 320) per 1,000 treated women.[186] In men, topiramate was better than placebo in a reduction of migraine attacks by 75 percent.[186]

Gabapentin

Presence of Aura

Gabapentin reduced migraine attack frequency and intensity significantly more than placebo, regardless of aura.[238] Patients with aura experienced slightly greater reduction in migraine frequency (mean difference -2.2, 95 percent CI, -2.7 to -1.7) than patients without aura (mean difference -1.6, 95 percent CI, -2.2 to -0.9). Patients with aura experienced slightly greater reduction in migraine intensity (mean difference -0.83, 95 percent, CI, -1.12 to -0.54) than patients without aura (mean difference -0.42, 95 percent CI, -0.77 to -0.07).

Antidepressants

Amitriptyline

Baseline Migraine Frequency

Amitriptyline was better than placebo in reducing monthly migraine only in patients with >17 migraine attacks per month (Appendix Table D169).[233] Amitriptyline was better than placebo in reducing monthly migraine only in depressed patients whose baseline migraine was frequent and severe (Appendix Table D170).[204]

A higher dose of amitriptyline increased the odds of reducing monthly migraine by ≥50 percent in accordance with increased baseline migraine days (odds ratio 2.35, 95 percent, CI 1.45 to 3.8 for every additional day of baseline migraine) (Appendix Table D171).[179]

Selective Calcium Channel Blockers

Nimodipine

Presence of Aura

A higher dose of nimodipine was not associated with increased response rates regardless of aura.[239] Nimodepin, 40 mg/day versus 20 mg/day, reduced use of drugs for acute attacks, but only in patients with classic and not common migraine.[239]

Discussion

Our report, in accordance with previously published reviews,[23, 24] demonstrated that all approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent. In addition, we found that off-label beta blockers and angiotensin acting drugs are more effective and safe than approved drugs in preventing adult migraine. The relative effect of drugs was moderate, with drugs resulting in 200 to 400 cases of clinical response (of ≥50 percent reduction in monthly migraine frequency) per 1,000 treated.

Critical assessment of the strength of the available evidence suggested low risk of bias in one-third and moderate risk of bias in more than half of included RCTs. We relied on direct evidence from head-to-head RCTs. We also analyzed previously published meta-analyses of individual patient data that provided valid estimation of dose response effects with drugs. However, strength of evidence was high only for topiramate, moderate for timolol and metoprolol, and low for other drugs due to risk of bias and imprecise estimates. Many authors of individual trials did not provide sufficient details about allocation concealment methods or about planned measurements of clinically important changes in quality of life scores and did not use intention-to-treat principles for all examined outcomes; nor did investigators fully adopt the recommendations from the Task Force of the International Headache Society Clinical Trials Subcommittee in design and reporting of the controlled clinical trials for preventing migraine in adults.[22]

We incorporated risk of bias in our evaluation of the strength of evidence, but we could not estimate the effect of risk of bias criteria on drug benefits or safety because most evidence came from individual RCTs. The role of financial conflict of interest and industry sponsor participation in data analyses and interpretation was difficult to evaluate due to inconsistent reporting in individual studies with no sufficient details.[240] For instance, the same authors disclosed no or different relationships with industry in multiple publications. Studies inconsistently reported subjects' baseline severity and frequency of migraine attacks as well as comorbidities and concomitant treatments.[2, 241]

Applicability of study population was good since trials enrolled predominantly middle- aged Caucasian women. However, average treatment effects in a clinically diverse population may not reflect the actual effects for a specific subgroup.[242] Very few studies provided evidence for individualized treatment decisions with clear descriptions of planned stratified randomization and subgroup analyses. Published RCTs rarely reported important patient characteristics that could modify drug effects (history of migraine, socioeconomic status, or response to prior preventive treatments).[243, 244] No trials examined the role of genetic polymorphism in drug metabolism and effects.[245-247]

A few RCTs reported treatment effects in patient subpopulations. Low strength of evidence suggested that botulinum toxin[227] and amitriptyline[179] were more effective in patients with frequent baseline migraine. Rates of migraine prevention varied from 1 to 50 percent in examined RCTs. Previous research demonstrated a high placebo response in trials aimed to treat acute migraine attacks.[28, 248] Our review demonstrated that a relative risk of adverse effects with botulinum toxin was lower in trials with higher placebo rates of adverse effects.[78] Previous research has demonstrated that patients with migraine quit taking topiramate due to bothersome adverse effects more often than patients with epilepsy.[28] Most trials in our review excluded patients with severe medical or psychiatric illnesses, stroke, and vascular migraine. Substantial variability in reporting comorbidities precluded using this information in quantitative synthesis of evidence.

Comparative effectiveness and safety with preventive drugs were examined in individual RCTs that failed to meet pooling criteria. Variability in examined drug comparisons in head-to-head RCTs precluded meta-analysis of direct evidence. However, indirect comparisons were feasible because we found no evident differences in baseline patient characteristics across RCTs. Thus, we conducted Bayesian network meta-analyses, which indicated that angiotensin acting drugs and beta blockers were the most effective and safe drugs. Head-to-head trials were not designed to test safety with migraine preventive drugs. Very few trials demonstrated significant increase in rates of bothersome adverse effects leading to treatment discontinuation when compared to placebo. In contrast, network meta-analysis demonstrated that patients stopped taking drugs more often with topiramate, divalproex, off-label antiepileptics, antidepressants, and ergot alkaloids than with placebo.

On average, rates of treatment discontinuation due to bothersome adverse effects were 6 percent with placebo, 6 percent with propranolol, 4 percent with off-label beta blockers, and 7 percent with flunarizine. In contrast, 15 percent of patients stopped taking topiramate, 12 percent stopped taking divalproex, 12 percent stopped taking antidepressants, and 10 percent stopped taking off-label antiepileptics. Individual adverse effects varied depending on the pharmacodynamic properties of the drugs. Multidisciplinary drug management programs demonstrated improvement in migraine-related disability and patient satisfaction, but long-term adherence and benefits are unclear.

Only a few RCTs examined quality of life, providing no consistent evidence of improvement with examined drugs. The authors rarely measured quality of life using disease-specific instruments such as the Migraine Specific Questionnaire, Migraine Disability Assessment, or the Headache Impact Test. We could not determine the clinical importance of statistically different changes in scores.

Our review has implications for clinical practice. Informed decisions in clinical settings should take into account exact rates of benefits and harms with specific drugs.[249] The most effective and safe drugs should be the first choice in adult migraine prevention. Our review demonstrated that approved beta blockers and off-label beta blockers and angiotensin acting drugs have better benefits and harms profiles than other drugs in RCTs. We could not find published controlled observational studies about preventive drug utilization and comparative effectiveness of approved versus off-label drugs. A single retrospective administrative database study found that migraine prophylaxis medications (tricyclic antidepressants, SSRI antidepressants, mirtazapine, venlafaxine, phenelzine, beta blockers, calcium channel blockers, valproic acid and derivatives, gabapentin, tiagabine, topiramate, and carbamazepine) were associated with a significant reduction in migraine-related costs.[250] Large observational studies of health care use for migraine did not analyze comparative effectiveness of preventive drugs.[5, 16]

Some evidence suggested that off-label drug utilization is common in the United States, despite having little or no scientific support.[21] For instance, the Institute of Medical Informatics Health National Disease and Therapeutic Index analysis suggested that 20 percent of all outpatient drug prescriptions for adults were for off-label drugs. The most commonly prescribed off-label drugs were anticonvulsants (46 percent), gabapentin (83 percent), and amitriptyline hydrochloride (81 percent).[251] We found that off-label antiepileptics and antidepressants demonstrated worse benefits and safety profiles than beta blockers or angiotensin acting drugs. Evidence of off-label drug use and associated adverse effects has been evaluated with prospective pharmacovigilance surveys in European countries.[252, 253] Routine monitoring of

harms with off-label drugs is needed in the United States in order to collect and analyze the comparative safety evidence in clinical settings.

Our report has limitations, including possible reporting bias. We restricted our review to studies published in English in journals, reviewed by the FDA, or reported on the ClinicalTrials.gov Web site. Even after such a comprehensive review of evidence, we do not know how many funded but unregistered studies we may have missed. Published articles rarely provided unique trial registration numbers from Clinicaltrials.gov. We concluded multiple reports of the same data based on available information and did not contact the authors for further clarifications. We suspected selective harms reporting because published articles reported common and expected adverse effects. In contrast, few RCTs that posted results in Clinicaltrials.gov reported all harms regardless of the rate or the assumed association with active drugs. We did not contact the authors requesting unreported benefits and harms. For studies in which methodological quality criteria were poorly reported, we did not contact the authors for additional details. Vast variability in examined treatment option, risk of bias, and imprecise estimates from small individual RCTs hampered synthesis of evidence.

We identified gaps and biases in available evidence that can direct future research (Table 38). Future randomized well-designed clinical trials should examine comparative effectiveness of the approved drugs and the most effective off-label ACE inhibitors, angiotensin II blockers, and off-label beta blockers. Future trials should examine the potential modification of treatment effects by factors such as patient age, sex, race, migraine family history, comorbidities, and prior treatment response. Observational studies should analyze off-label drug use as well as the comparative effectiveness and safety of migraine preventive drugs. Analysis of administrative databases should examine visits to doctors and emergency rooms among adults taking migraine preventive drugs. Prospective pharmacovigilance methods should be used for routine monitoring of off-label drug utilization and associated adverse effects with migraine preventive drugs. All interventional studies should be registered in Clinicaltrials.gov. All clinical trials of migraine preventive drugs should be required to post their results in Clinicaltrials.gov.

Key Messages

Efficacy and Comparative Effectiveness of Pharmacological Treatments for Preventing Migraine Attacks in Adults

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Placebo or No Active Treatment

- All approved drugs, off-label beta blockers, and ACE inhibitors were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response).
- Relative effect of drugs was moderate: drugs resulted in clinical response in 200 to 400 patients per 1,000 treated.
- Only one off-label drug, captopril, resulted in clinical response in more than 500 patients per 1,000 treated.
- Strength of evidence was high for topiramate, moderate for timolol and metoprolol, and low for other drugs due to risk of bias and imprecise estimates.

- Low strength of evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of botulinum toxin, topiramate (from 50-100 mg with no additional benefits with 200 mg/day), pindolol, nadolol, bisoprolol, and venlafaxine.

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Active Pharmacological Treatments

- Individual RCTs provided low strength of evidence about the comparative effectiveness of drugs and demonstrated few significant differences.
- Strength of evidence was low for all direct comparisons.
- Network Bayesian meta-analysis of 84 RCTs with 41 different drugs from 13 drug classes demonstrated that ACE inhibitors, angiotensin II receptor antagonists, propranolol, and off-label beta blockers are more effective than all other drugs.

Effect of Preventive Pharmacological Treatments on Patient-centered and Intermediate Outcomes Compared to Active Nonpharmacological Treatments

- Individual RCTs provided low strength of evidence that reduction of ≥50 percent in monthly migraine attacks did not differ with propranolol versus biofeedback or amitriptyline versus spinal manipulation.

Influence of Approaches to Drug Management (Such as Patient Care Teams, Integrated Care, Coordinated Care, Patient Education, Drug Surveillance, or Interactive Drug Monitoring)

- Multidisciplinary team care improved quality of life and reduced migraine-related disability.
- Headache management program resulted in complete cessation of migraine.
- Cognitive-behavioral minimal contact program improved patient satisfaction with treatments.
- Headache school decreased overuse of acute drugs and reduced migraine disability.
- Pharmaceutical care improved mental health and self-efficacy.
- Intensive pharmaceutical care campaign had no statistically significant impact on use of drugs for acute attacks.

Comparative Harms From Pharmacological Treatments for Preventing Migraine Attacks in Adults

- Bothersome adverse effects leading to treatment discontinuation were examined in 52 RCTs with 28 different drugs from eight drug classes.
- Moderate strength of evidence suggested that topiramate and botulinum toxin resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- The association was dose responsive for topiramate.

- Among other drugs, acetazolamide and lamotrigine resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- Limited low strength evidence from individual head-to-head RCTs suggested that propranolol was safer than nifedipine and metoprolol was safer than clomipramine.
- Bayesian network meta-analysis suggested that topiramate, divalproex, off-label antiepileptic, antidepressants, and ergot alkaloids increased the rates of bothersome adverse effects leading to treatment discontinuation.
- Divalproex and off label antiepileptic resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.

Influence of Patient Characteristics on the Effectiveness and Safety of Pharmacological Treatments for Preventing Migraine Attacks in Adults

- Evidence was limited to individual RCTs that examined the drug effect modification by selected patient characteristics.
- Botulinum toxin was better than placebo in reducing monthly migraine attacks by ≥50 percent irrespective of placebo response, but magnitude of the effect was slightly larger in placebo nonresponders. Botulinum toxin was more effective in patients with a higher mean baseline migraine frequency.
- Amitriptyline was better than placebo in reducing monthly migraine only in patients with >17 migraine attacks per month and in depressed patients with severe migraine at baseline.

Table 38. Future research needs

Key Question	Findings	Types of studies needed to answer question	Future research recommendation
KQ1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults?	• All approved drugs, off-label beta blockers and ACE inhibitors were better than placebo in reducing monthly migraine frequency by ≥50% (clinical response) • Individual RCTs provided low strength of evidence about comparative effectiveness of drugs with few significant differences. • Network Bayesian meta-analysis of 84 RCTs with 41 different drugs from 13 drug classes demonstrated that ACE inhibitors, angiotensin II receptor antagonists, propranolol, and off label beta blockers are more effective than all other drugs.	• Randomized clinical trials. • Creating of migraine registry with individual patient data from electronic medical records and quarterly completed migraine diaries. • Analysis of health insurance, Medicare, and Medicaid databases. • Prospective pharmacovigilance surveys.	• Design low risk of bias RCTs following recommendations from the HIS about migraine definitions, inclusion, and exclusion criteria of the subjects, assessments of patient centered outcomes at the end of the treatments and at 6 months or more of followup. • Conduct observational studies reducing risk of bias by matching, adjustment, and propensity score. • Examine comparative effectiveness of the most effective and safe angiotensin acting drugs and beta blockers with approved antiepileptics. • Examine treatment effects in patient subpopulations by age, gender, race, socioeconomic status, prior treatment history, comorbidity, family history of migraine, and baseline migraine type, severity, and frequency. • Focus on validated measures of quality of life and migraine related disability. • Examined preventive drug utilization and the effects on health care utilization (emergency visits, hospitalizations, abortive drug utilization and overuse). • Examine which patient and provider characteristics are associated with preventive drug utilization. • Examine the benefits with multidisciplinary migraine management programs and combined pharmacological and self-administrated migraine management interventions.
KQ2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults?	• Moderate strength of evidence suggested that topiramate and botulinum toxin resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. • Among other drugs, acetazolamide and lamotrigine resulted in bothersome adverse effects leading to	• Randomized clinical trials. • Creating of migraine registry with individual patient data from electronic medical records and quarterly completed migraine diaries. • Analysis of health insurance, Medicare, and Medicaid databases. • Prospective pharmacovigilance surveys	• Design low risk of bias fully powered to assess harms RCTs following recommendations from the HIS about migraine definitions, inclusion, and exclusion criteria of the subjects, comorbidities, assessments of patient centered outcomes at the end of the treatments and at 6 months or more of followup. • Conduct observational studies reducing risk of bias by matching, adjustment, and propensity score. • Examine comparative safety of the commonly used approved and off label drugs with the most effective

Table 38. Future research needs (continue)

Key Question	Findings	Types of studies needed to answer question	Future research recommendation
	treatment discontinuation more often than placebo. • Limited low strength evidence from individual head-to-head RCTs suggested that propranolol was safer than nifedipine and metoprolol was safer than clomipramine • Bayesian network meta-analysis suggested that topiramate, divalproex, off label antiepileptic, antidepressants, and ergot alkaloids increased the rates of bothersome adverse effects leading to treatment discontinuation. • Divalproex and off label antiepileptic resulted in bothersome adverse effects leading to treatment discontinuation more often than beta blockers.		and safe angiotensin acting drugs and beta blockers. • Examine treatment harms in patient subpopulations by age, sex, race, socioeconomic status, prior treatment history, comorbidity, concomitant treatments, family history of migraine, and doses of the drugs. • Analyze all harms the patient experienced irrespective of investigator determination about causality between drugs and harms. • Examined preventive drug utilization and the effects on health care utilization (treatments for adverse effects, hospitalizations for drug harms). • Examine the effects of multidisciplinary migraine management programs on patient safety. • Routinely analyze all harms in patients with migraine taking preventive drugs.
KQ3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?	• Evidence was limited to individual RCTs that examined the drug effect modification by selected patient characteristics.	• Randomized clinical trials. • Creating of migraine registry with individual patient data from electronic medical records and quarterly completed migraine diaries. • Analysis of health insurance, Medicare, and Medicaid databases; prospective pharmacovigilance surveys.	• Conduct low risk of bias RCTs with planned subgroup analysis of treatment benefits by age, sex, race, socioeconomic status, prior treatment history, comorbidity, family history of migraine, and baseline migraine type, severity, and frequency. • Conduct low risk of bias powered RCTs with planned subgroup analysis of treatment harms by age, sex, race, socioeconomic status, prior treatment history, comorbidity, concomitant treatments, family history of migraine, and doses of the drugs. • Conduct pharmacogenomic studies to examine the effects of genetically predisposed drug metabolism on treatment benefits and harms. • Evaluate treatment effects in patient subpopulations by age, sex, race, socioeconomic status, prior treatment history, comorbidity, family history of migraine, and baseline migraine type, severity, and

Table 38. Future research needs (continue)

Key Question	Findings	Types of studies needed to answer question	Future research recommendation
			frequency. • Examine treatment harms in patient subpopulations by age, sex, race, socioeconomic status, prior treatment history, comorbidity, concomitant treatments, family history of migraine, and doses of the drugs. • Routinely analyze which patient and provider characteristics are associated with drug adverse effects in patients with migraine taking preventive drugs. • Routinely analyze which patient and provider characteristics are associated with treatment discontinuation in patients with migraine taking preventive drugs.

References

1. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
2. Silberstein SD. Preventive migraine treatment. Neurol Clin. 2009 May;27(2):429-43. PMID 19289224.
3. Solomon GD, Santanello N. Impact of migraine and migraine therapy on productivity and quality of life. Neurology. 2000;55(9 Suppl 2):S29-35. PMID 11089517.
4. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007 Mar;47(3):355-63. PMID 17371352.
5. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002 Mar 26;58(6):885-94. PMID 11914403.
6. Bigal ME, Lipton RB, Winner P, et al. Migraine in adolescents: association with socioeconomic status and family history. Neurology. 2007 Jul 3;69(1):16-25. PMID 17606878.
7. Hernandez-Latorre MA, Roig M. Natural history of migraine in childhood. Cephalalgia. 2000 Jul;20(6):573-9. PMID 11075841.
8. Charles A. Advances in the basic and clinical science of migraine. Ann Neurol. 2009 May;65(5):491-8. PMID 19479724.
9. Lipton RB, Bigal ME, Diamond M, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007 Jan 30;68(5):343-9. PMID 17261680.
10. Natoli JL, Manack A, Dean B, et al. Global prevalence of chronic migraine: a systematic review. Cephalalgia. 2010 May;30(5):599-609. PMID 19614702.
11. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID 16686915.
12. Solomon S. New appendix criteria open for a broader concept of chronic migraine (Comment on: Cephalagia 2006 Jun:26(6):742-6). Cephalalgia. 2007 May;27(5):469; author reply -70. PMID 17448186.
13. Stewart WF, Ricci JA, Chee E, et al. Lost productive work time costs from health conditions in the United States: results from the American Productivity Audit. J Occup Environ Med. 2003 Dec;45(12):1234-46. PMID 14665809.
14. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. Arch Intern Med. 1999 Apr 26;159(8):813-8. PMID 10219926.
15. Burton WN, Landy SH, Downs KE, et al. The impact of migraine and the effect of migraine treatment on workplace productivity in the United States and suggestions for future research. Mayo Clin Proc. 2009 May;84(5):436-45. PMID 19411440.
16. Lipton RB, Scher AI, Steiner TJ, et al. Patterns of health care utilization for migraine in England and in the United States. Neurology. 2003 Feb 11;60(3):441-8. PMID 12578925.
17. Lipton RB, Stewart WF. The epidemiology of migraine. Eur Neurol. 1994;34 Suppl 2:6-11. PMID 7835383.
18. Sprenger T, Goadsby PJ. Migraine pathogenesis and state of pharmacological treatment options. BMC Medicine. 2009;7:71. PMID 19917094.
19. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. Curr Opin Neurol. 2006 Jun;19(3):294-8. PMID 16702838.
20. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. Neurol Sci. 2008 May;29 Suppl 1:S110-22. PMID 18545911.
21. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427-9. PMID 18385495.
22. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008 May;28(5):484-95. PMID 18294250.
23. Schroeder BM. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. Am Fam Physician. 2003 Mar 15;67(6):1392, 5-7. PMID 12674472.
24. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. 2000 2000 Nov 15;62(10):2359-60. PMID 11126860.

25. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62. PMID 10993991.
26. Schuurmans A, van Weel C. Pharmacologic treatment of migraine. Comparison of guidelines. Can Fam Physician. 2005 Jun;51:838-43. PMID 15986940.
27. Lainez MJ, Freitag FG, Pfeil J, et al. Time course of adverse events most commonly associated with topiramate for migraine prevention. Eur J Neurol. 2007 Aug;14(8):900-6. PMID 17662012.
28. Luykx J, Mason M, Ferrari MD, et al. Are migraineurs at increased risk of adverse drug responses? A meta-analytic comparison of topiramate-related adverse drug reactions in epilepsy and migraine. Clin Pharmacol Ther. 2009 Mar;85(3):283-8. PMID 18987621.
29. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63(12):2215-24. PMID 15623677.
30. Gunner KB, Smith HD, Ferguson LE. Practice guideline for diagnosis and management of migraine headaches in children and adolescents: Part two. J Pediatr Health Care. 2008 Jan-Feb;22(1):52-9. PMID 18174091.
31. Geraud G, Lanteri-Minet M, Lucas C, et al. French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther. 2004 Aug;26(8):1305-18. PMID 15476911.
32. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. PMID 19708964.
33. Dowson AJ, Lipscombe S, Sender J, et al. New guidelines for the management of migraine in primary care. Curr Med Res Opin. 2002;18(7):414-39. PMID 12487508.
34. U.S. Food and Drug Administration. FDA News Release: FDA Approves Botox to Treat Chronic Migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.
35. Amanzio M, Corazzini LL, Vase L, et al. A systematic review of adverse events in placebo groups of anti-migraine clinical trials. Pain. 2009 Dec;146(3):261-9. PMID 19781854.
36. Whyte CA, Tepper SJ. Adverse effects of medications commonly used in the treatment of migraine. Expert Rev Neurother. 2009 Sep;9(9):1379-91. PMID 19769452.
37. Whitlock EP, Lopez SA, Chang S, et al. AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):491-501. PMID 19540721.
38. Slutsky J, Atkins D, Chang S, et al. Comparing medical interventions: AHRQ and the Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. 2011/03/25 ed. Vol. March 2011. Rockville, MD: Agency for Healthcare Research and Quality; 2008:1-4. Available at www.effectivehealthcare.ahrq.gov.
39. Helfand M, Balshem H. Principles in Developing and Applying Guidance. 2008PMID 21433405.
40. Shamilyan T. Comparative effectiveness of preventive pharmacological treatments for migraine in adults. Prospero. 2011PMID CRD42012001918.
41. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine. 2009 Aug 18;151(4):W65-94. PMID 19622512.
42. White CM, Ip S, McPheeters ML, et al. Chapter 11. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Resarch and Quality: March 2011; 2009:136-51. Available at www.effectivehealthcare.ahrq.gov.
43. Norris S, Atkins D, Bruening W, et al. Chapter 4. Selecting observational studies for comparing medical interventions. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:56-68. Available at: www.effectivehealthcare.ahrq.gov.

44. Higgins J, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration; 2011.
45. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2008 Sep 25;63(5):502-12. PMID 18823754.
46. Rothner AD. Complicated migraine and migraine variants. Curr Pain Headache Rep. 2002 Jun;6(3):233-9. PMID 12003695.
47. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160. PMID 14979299.
48. Hansen JM, Thomsen LL, Olesen J, et al. Calcitonin gene-related peptide does not cause the familial hemiplegic migraine phenotype. Neurology. 2008 Sep 9;71(11):841-7. PMID 18779512.
49. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID 22008217.
50. Viswanathan M AM, Berkman ND, Chang S, Hartling L, McPheeters LM, Santaguida PL, Shamliyan T, Singh K, Tsertsvadze A, Treadwell JR. Assessing the Risk of Bias of Individual Studies in Systematic Reviews of Health Care Interventions. Agency for Healthcare Research and Quality Methods Guide for Comparative Effectiveness Reviews. 2012;AHRQ Publication No. 12-EHC047-EF.(Available at: www.effectivehealthcare.ahrq.gov/).
51. Viswanathan M BN. Development of the RTI Item Bank on Risk of Bias and Precision of Observational Studies.
. Methods Research Report. (Prepared by the RTI International–University of North Carolina Evidence-based Practice Center under Contract No. 290-2007-0056-I.) 2011;AHRQ Publication No. 11-EHC028-EF. Rockville, MD: Agency for Healthcare Research and Quality(Available at: www.effectivehealthcare.ahrq.gov/reports/final.cfm.).
52. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID 19595577.
53. Guyatt G, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol. 2011 Aug 10PMID 21839614.
54. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID 21784880.
55. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Sudbury, MA: Jones and Bartlett; 2003.
56. van der Velde G, van Tulder M, Cote P, et al. The sensitivity of review results to methods used to appraise and incorporate trial quality into data synthesis. Spine (Phila Pa 1976). 2007 Apr 1;32(7):796-806. PMID 17414916.
57. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006 Dec;59(12):1249-56. PMID 17098567.
58. Ad Hoc Committee on Classification of Headache. Classification of headache. JAMA. 1962;179(9):717-8.
59. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol. 2009;9:80. PMID 19961608.
60. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001.
61. Fu R, Gartlehner G, Grant M, et al. Chapter 9. Conducting quantitative synthesis when comparing medical interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:104-19. Available at: http://effectivehealthcare.ahrq.gov.
62. Rucker G, Schwarzer G, Carpenter J, et al. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. Stat Med. 2009 Feb 28;28(5):721-38. PMID 19072749.

63. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53-77. PMID 16596572.
64. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351-75. PMID 15116347.
65. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med. 2010 Dec 20;29(29):3046-67. PMID 20827667.
66. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. Stat Med. 2007 Jan 15;26(1):37-52. PMID 16463355.
67. Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. Biom J. 2006 Apr;48(2):271-85. PMID 16708778.
68. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID 3802833.
69. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. Eval Health Prof. 2001 Jun;24(2):152-64. PMID 11523384.
70. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998 Nov 7;317(7168):1309-12. PMID 9804726.
71. Carlin BP, Louis TA. Bayesian Methods for Data Analysis. Boca Raton, Fla.: Chapman & Hall/CRC; 2009.
72. Glenny AM, Altman DG, Song F, et al. Indirect comparisons of competing interventions. Health Technol Assess. 2005 Jul;9(26):1-134, iii-iv. PMID 16014203.
73. Slutsky J, Atkins D, Chang S, et al. AHRQ series paper 1: comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):481-3. PMID 18834715.
74. Helfand M, Balshem H. AHRQ series paper 2: principles for developing guidance: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):484-90. PMID 19716268.
75. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35. PMID 11306229.
76. Silberstein S, Mathew N, Saper J, et al. Botulinum toxin type A as a migraine preventive treatment. For the BOTOX Migraine Clinical Research Group. Headache. 2000 Jun;40(6):445-50. PMID 10849039.
77. Freitag FG, Diamond S, Diamond M, et al. Botulinum Toxin Type A in the treatment of chronic migraine without medication overuse. Headache. 2008 Feb;48(2):201-9. PMID 18042229.
78. Mathew NT, Frishberg BM, Gawel M, et al. Botulinum toxin type A (BOTOX) for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Apr;45(4):293-307. PMID 15836565.
79. Anand KS, Prasad A, Singh MM, et al. Botulinum toxin type A in prophylactic treatment of migraine. Am J Ther. 2006 May-Jun;13(3):183-7. PMID 16772757.
80. Vo AH, Satori R, Jabbari B, et al. Botulinum toxin type-a in the prevention of migraine: a double-blind controlled trial. Aviat Space Environ Med. 2007 May;78(5 Suppl):B113-8. PMID 17547312.
81. Chankrachang S, Arayawichanont A, Poungvarin N, et al. Prophylactic botulinum type A toxin complex (Dysport(R)) for migraine without aura. Headache. 2011 Jan;51(1):52-63. PMID 21083558.
82. Cady R, Schreiber C. Botulinum toxin type A as migraine preventive treatment in patients previously failing oral prophylactic treatment due to compliance issues. Headache. 2008 Jun;48(6):900-13. PMID 18047501.
83. Saper JR, Lake AE, 3rd, Cantrell DT, et al. Chronic daily headache prophylaxis with tizanidine: a double-blind, placebo-controlled, multicenter outcome study. Headache. 2002 Jun;42(6):470-82. PMID 12167135.
84. Silberstein SD, Hulihan J, Karim MR, et al. Efficacy and tolerability of topiramate 200 mg/d in the prevention of migraine with/without aura in adults: a randomized, placebo-controlled, double-blind, 12-week pilot study. Clin Ther. 2006 Jul;28(7):1002-11. PMID 16990078.
85. Silvestrini M, Bartolini M, Coccia M, et al. Topiramate in the treatment of chronic migraine. Cephalalgia. 2003 Oct;23(8):820-4. PMID 14510929.

86. Diener HC, Agosti R, Allais G, et al. Cessation versus continuation of 6-month migraine preventive therapy with topiramate (PROMPT): a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2007 Dec;6(12):1054-62. PMID 17988947.
87. Brandes JL, Kudrow DB, Rothrock JF, et al. Assessing the ability of topiramate to improve the daily activities of patients with migraine. Mayo Clin Proc. 2006 Oct;81(10):1311-9. PMID 17036556.
88. Diener HC, Bussone G, Van Oene JC, et al. Topiramate reduces headache days in chronic migraine: a randomized, double-blind, placebo-controlled study. Cephalalgia. 2007 Jul;27(7):814-23. PMID 17441971.
89. Dahlof C, Loder E, Diamond M, et al. The impact of migraine prevention on daily activities: a longitudinal and responder analysis from three topiramate placebo-controlled clinical trials. Health Qual Life Outcomes. 2007;5:56. PMID 17916258.
90. Freitag FG, Collins SD, Carlson HA, et al. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. Neurology. 2002 Jun 11;58(11):1652-9. PMID 12058094.
91. Mathew NT, Saper JR, Silberstein SD, et al. Migraine prophylaxis with divalproex. Arch Neurol. 1995 Mar;52(3):281-6. PMID 7872882.
92. Klapper J. Divalproex sodium in migraine prophylaxis: a dose-controlled study. Cephalalgia. 1997 Apr;17(2):103-8. PMID 9137847.
93. Jensen R, Brinck T, Olesen J. Sodium valproate has a prophylactic effect in migraine without aura: a triple-blind, placebo-controlled crossover study. Neurology. 1994 Apr;44(4):647-51. PMID 8164818.
94. Hering R, Kuritzky A. Sodium valproate in the prophylactic treatment of migraine: a double-blind study versus placebo. Cephalalgia. 1992 Apr;12(2):81-4. PMID 1576648.
95. Diener HC, Tfelt-Hansen P, Dahlof C, et al. Topiramate in migraine prophylaxis--results from a placebo-controlled trial with propranolol as an active control. J Neurol. 2004 Aug;251(8):943-50. PMID 15316798.
96. Wideroe TE, Vigander T. Propranolol in the treatment of migraine. Br Med J. 1974 Jun 29;2(5921):699-701. PMID 4604977.
97. Tfelt-Hansen P, Standnes B, Kangasneimi P, et al. Timolol vs propranolol vs placebo in common migraine prophylaxis: a double-blind multicenter trial. Acta Neurol Scand. 1984 Jan;69(1):1-8. PMID 6367336.
98. Ahuja GK, Verma AK. Propranolol in prophylaxis of migraine. Indian J Med Res. 1985 Sep;82:263-5. PMID 3908306.
99. Forssman B, Henriksson KG, Johannsson V, et al. Propranolol for migraine prophylaxis. Headache; 1976. p. 238-45.
100. Standnes B. The prophylactic effect of timolol versus propranolol and placebo in common migraine: Beta-blockers in migraine. Cephalalgia; 1982. p. 165-70.
101. Stellar S, Ahrens SP, Meibohm AR, et al. Migraine prevention with timolol. A double-blind crossover study. JAMA. 1984 Nov 9;252(18):2576-80. PMID 6387197.
102. Calandre EP, Garcia-Leiva JM, Rico-Villademoros F, et al. Pregabalin in the treatment of chronic migraine: an open-label study. Clinical Neuropharmacology. 2010 Jan-Feb;33(1):35-9. PMID 19935409.
103. Kangasniemi P, Andersen AR, Andersson PG, et al. Classic migraine: effective prophylaxis with metoprolol. Cephalalgia. 1987 Dec;7(4):231-8. PMID 3322569.
104. Andersson PG, Dahl S, Hansen JH, et al. Prophylactic treatment of classical and non-classical migraine with metoprolol--a comparison with placebo. Cephalalgia. 1983 Dec;3(4):207-12. PMID 6640652.
105. Siniatchkin M, Andrasik F, Kropp P, et al. Central mechanisms of controlled-release metoprolol in migraine: a double-blind, placebo-controlled study. Cephalalgia. 2007 Sep;27(9):1024-32. PMID 17680819.
106. Forssman B. Atenolol for Migraine Prophylaxis. Acta Neurologica Scandinavica. 1982;65(S90):75-6.
107. Freitag FG, Diamond S. Nadolol and placebo comparison study in the prophylactic treatment of migraine. The Journal of the American Osteopathic Association; 1984. p. 343-7.
108. Ekbom K. Alprenolol for migraine prophylaxis. Headache; 1975. p. 129-32.
109. Sjaastad O, Stensrud P. Clinical trial of a beta-receptor blocking agent (LB 46) in migraine prophylaxis. Acta neurologica Scandinavica; 1972. p. 124-8.
110. Couch JR, Hassanein RS. Migraine and depression: effect of amitriptyline prophylaxis. Trans Am Neurol Assoc; 1976. p. 234-7.
111. Adly C, Straumanis J, Chesson A. Fluoxetine prophylaxis of migraine. Headache. 1992 Feb;32(2):101-4. PMID 1551787.

112. Goadsby PJ, Ferrari MD, Csanyi A, et al. Randomized, double-blind, placebo-controlled, proof-of-concept study of the cortical spreading depression inhibiting agent tonabersat in migraine prophylaxis. Cephalalgia. 2009 Jul;29(7):742-50. PMID 19222510.
113. Ozyalcin SN, Talu GK, Kiziltan E, et al. The efficacy and safety of venlafaxine in the prophylaxis of migraine. Headache. 2005 Feb;45(2):144-52. PMID 15705120.
114. Havanka-Kanniainen H, Hokkanen E, Myllylä VV. Efficacy of nimodipine in the prophylaxis of migraine. Cephalalgia : an international journal of headache; 1985. p. 39-43.
115. Gelmers HJ. Nimodipine, a new calcium antagonist, in the prophylactic treatment of migraine. Headache; 1983. p. 106-9.
116. Leandri M, Rigardo S, Schizzi R, et al. Migraine treatment with nicardipine. Cephalalgia. 1990 Jun;10(3):111-6. PMID 2245455.
117. Markley HG, Cheronis JC, Piepho RW. Verapamil in prophylactic therapy of migraine. Neurology; 1984. p. 973-6.
118. Solomon GD, Steel JG, Spaccavento LJ. Verapamil prophylaxis of migraine. A double-blind, placebo-controlled study. JAMA. 1983 Nov 11;250(18):2500-2. PMID 6355533.
119. Schrader H, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with angiotensin converting enzyme inhibitor (lisinopril): randomised, placebo controlled, crossover study. BMJ. 2001 Jan 6;322(7277):19-22. PMID 11141144.
120. Minervini MG, Pinto K. Captopril relieves pain and improves mood depression in depressed patients with classical migraine. Cephalalgia; 1987. p. 485-6.
121. Tronvik E, Stovner LJ, Helde G, et al. Prophylactic treatment of migraine with an angiotensin II receptor blocker: a randomized controlled trial. JAMA. 2003 Jan 1;289(1):65-9. PMID 12503978.
122. Diener HC, Gendolla A, Feuersenger A, et al. Telmisartan in migraine prophylaxis: a randomized, placebo-controlled trial. Cephalalgia. 2009 Sep;29(9):921-7. PMID 19250283.
123. Behan PO. Prophylactic treatment for migraine - a comparison of pizotifen and clonidine. Cephalalgia; 1985. p. 524-5.
124. Ryan RE, Diamond S. Double blind study of clonidine and placebo for the prophylactic treatment of migraine. Headache; 1975. p. 202-10.
125. Adam EI, Gore SM, Price WH. Double blind trial of clonidine in the treatment of migraine in a general practice. J R Coll Gen Pract. 1978 Oct;28(195):587-90. PMID 368333.
126. Bredfeldt RC, Sutherland JE, Kruse JE. Efficacy of transdermal clonidine for headache prophylaxis and reduction of narcotic use in migraine patients. A randomized crossover trial. J Fam Pract. 1989 Aug;29(2):153-6; discussion 7-8. PMID 2666565.
127. Elkind AH, Webster C, Herbertson Jr RK. Efficacy of guanfacine in a double blind parallel study for migraine prophylaxis. Cephalalgia; 1989. p. 369-70.
128. Pradalier A, Lanteri-Minet M, Geraud G, et al. The PROMISE study: PROphylaxis of MIgraine with SEglor (dihydroergotamine mesilate) in French primary care. CNS Drugs. 2004;18(15):1149-63. PMID 15581385.
129. Brandes JL, Visser WH, Farmer MV, et al. Montelukast for migraine prophylaxis: a randomized, double-blind, placebo-controlled study. Headache. 2004 Jun;44(6):581-6. PMID 15186302.
130. Krymchantowski AV, Jevoux C, Moreira PF. An open pilot study assessing the benefits of quetiapine for the prevention of migraine refractory to the combination of atenolol, nortriptyline, and flunarizine. Pain Med. 2010 Jan;11(1):48-52. PMID 20002594.
131. Charles A, Flippen C, Romero Reyes M, et al. Memantine for prevention of migraine: a retrospective study of 60 cases. J Headache Pain. 2007 Sep;8(4):248-50. PMID 17901918.
132. Spengos K, Theleritis C, Paparrigopoulos T. Memantine and NMDA antagonism for chronic migraine: a potentially novel therapeutic approach? Headache. 2008 Feb;48(2):284-6. PMID 18194287.
133. Mathew NT, Jaffri SF. A double-blind comparison of onabotulinumtoxina (BOTOX) and topiramate (TOPAMAX) for the prophylactic treatment of chronic migraine: a pilot study. Headache. 2009 Nov-Dec;49(10):1466-78. PMID 19912346.
134. Blumenfeld AM, Schim JD, Chippendale TJ. Botulinum toxin type A and divalproex sodium for prophylactic treatment of episodic or chronic migraine. Headache. 2008 Feb;48(2):210-20. PMID 18047502.
135. Magalhaes E, Menezes C, Cardeal M, et al. Botulinum toxin type A versus amitriptyline for the treatment of chronic daily migraine. Clin Neurol Neurosurg. 2010 Jul;112(6):463-6. PMID 20399553.

136. Cady RK, Schreiber CP, Porter JA, et al. A multi-center double-blind pilot comparison of onabotulinumtoxinA and topiramate for the prophylactic treatment of chronic migraine. Headache. 2011 Jan;51(1):21-32. PMID 21070228.
137. Dodick DW, Freitag F, Banks J, et al. Topiramate versus amitriptyline in migraine prevention: a 26-week, multicenter, randomized, double-blind, double-dummy, parallel-group noninferiority trial in adult migraineurs. Clin Ther. 2009 Mar;31(3):542-59. PMID 19393844.
138. Gupta P, Singh S, Goyal V, et al. Low-dose topiramate versus lamotrigine in migraine prophylaxis (the Lotolamp study). Headache. 2007 Mar;47(3):402-12. PMID 17371357.
139. Mohammadianinejad SE, Abbasi V, Sajedi SA, et al. Zonisamide versus topiramate in migraine prophylaxis: a double-blind randomized clinical trial. Clin Neuropharmacol. 2011 Jul-Aug;34(4):174-7. PMID 21738025.
140. Bartolini M, Silvestrini M, Taffi R, et al. Efficacy of topiramate and valproate in chronic migraine. Clin Neuropharmacol. 2005 Nov-Dec;28(6):277-9. PMID 16340383.
141. de Tommaso M, Marinazzo D, Nitti L, et al. Effects of levetiracetam vs topiramate and placebo on visually evoked phase synchronization changes of alpha rhythm in migraine. Clin Neurophysiol. 2007 Oct;118(10):2297-304. PMID 17709295.
142. Ashtari F, Shaygannejad V, Akbari M. A double-blind, randomized trial of low-dose topiramate vs propranolol in migraine prophylaxis. Acta Neurol Scand. 2008 Nov;118(5):301-5. PMID 18713156.
143. Togha M, Rahmat Jirde M, Nilavari K, et al. Cinnarizine in refractory migraine prophylaxis: efficacy and tolerability. A comparison with sodium valproate. J Headache Pain. 2008 Apr;9(2):77-82. PMID 18286231.
144. Kaniecki RG. A comparison of divalproex with propranolol and placebo for the prophylaxis of migraine without aura. Arch Neurol. 1997 Sep;54(9):1141-5. PMID 9311358.
145. Kass B, Nestvold K. Propranolol (Inderal) and clonidine (Catapressan) in the prophylactic treatment of migraine. A comparative trial. Acta Neurol Scand. 1980 Jun;61(6):351-6. PMID 6998250.
146. Olerud B, Gustavsson CL, Furberg B. Nadolol and propranolol in migraine management. Headache; 1986. p. 490-3.
147. Kangasniemi P, Hedman C. Metoprolol and propranolol in the prophylactic treatment of classical and common migraine. A double-blind study. Cephalalgia. 1984 Jun;4(2):91-6. PMID 6428749.
148. Gerber WD, Diener HC, Scholz E, et al. Responders and non-responders to metoprolol, propranolol and nifedipine treatment in migraine prophylaxis: a dose-range study based on time-series analysis. Cephalalgia. 1991 Feb;11(1):37-45. PMID 2036669.
149. Sudilovsky A, Elkind AH, Ryan RES, et al. Comparative efficacy of nadolol and propranolol in the management of migraine. Headache; 1987. p. 421-6.
150. Albers GW, Simon LT, Hamik A, et al. Nifedipine versus propranolol for the initial prophylaxis of migraine. Headache. 1989 Apr;29(4):215-8. PMID 2654067.
151. Ziegler DK, Hurwitz A, Hassanein RS, et al. Migraine prophylaxis. A comparison of propranolol and amitriptyline. Arch Neurol. 1987 May;44(5):486-9. PMID 3579659.
152. Domingues RB, Silva AL, Domingues SA, et al. A double-blind randomized controlled trial of low doses of propranolol, nortriptyline, and the combination of propranolol and nortriptyline for the preventive treatment of migraine. Arq Neuropsiquiatr. 2009 Dec;67(4):973-7. PMID 20069203.
153. Kangasniemi PJ, Nyrke T, Lang AH, et al. Femoxetine - a new 5-HT uptake inhibitor - and propranolol in the prophylactic treatment of migraine. Acta Neurol Scand; 1983. p. 262-7.
154. Worz R, Reinhardt-Benmalek B, Foeh M, et al. Migraine prophylaxis with bisoprolol. Headache Quarterly; 1992. p. 64-72.
155. Worz R, Reinhardt-Benmalek B, Grotemeyer KH, et al. Bisoprolol and metoprolol in the prophylactic treatment of migraine with and without aura - A randomized double-blind cross-over multicenter study. Cephalalgia; 1991. p. 152-3.
156. Schellenberg R, Lichtenthal A, Wohling H, et al. Nebivolol and metoprolol for treating migraine: an advance on beta-blocker treatment? Headache. 2008 Jan;48(1):118-25. PMID 18184294.
157. Grotemeyer KH, Scharafinski HW, Schlake HP, et al. Acetylsalicylic acid vs. metoprolol in migraine prophylaxis--a double-blind cross-over study. Headache. 1990 Oct;30(10):639-41. PMID 2272812.

158. Diener HC, Hartung E, Chrubasik J, et al. A comparative study of oral acetylsalicyclic acid and metoprolol for the prophylactic treatment of migraine. A randomized, controlled, double-blind, parallel group phase III study. Cephalalgia. 2001 Mar;21(2):120-8. PMID 11422094.
159. Louis P, Schoenen J, Hedman C. Metoprolol v. clonidine in the prophylactic treatment of migraine. Cephalalgia. 1985 Sep;5(3):159-65. PMID 3899370.
160. Krymchantowski AV, Silva MT, Barbosa JS, et al. Amitriptyline versus amitriptyline combined with fluoxetine in the preventative treatment of transformed migraine: a double-blind study. Headache. 2002 Jun;42(6):510-4. PMID 12167139.
161. Bank J. A comparative study of amitriptyline and fluvoxamine in migraine prophylaxis. Headache. 1994 Sep;34(8):476-8. PMID 7960733.
162. Bulut S, Berilgen MS, Baran A, et al. Venlafaxine versus amitriptyline in the prophylactic treatment of migraine: randomized, double-blind, crossover study. Clin Neurol Neurosurg. 2004 Dec;107(1):44-8. PMID 15567552.
163. Tarlaci S. Escitalopram and venlafaxine for the prophylaxis of migraine headache without mood disorders. Clin Neuropharmacol. 2009 Sep-Oct;32(5):254-8. PMID 19667978.
164. Kaushik R, Kaushik RM, Mahajan SK, et al. Biofeedback assisted diaphragmatic breathing and systematic relaxation versus propranolol in long term prophylaxis of migraine. Complement Ther Med. 2005 Sep;13(3):165-74. PMID 16150370.
165. Nelson CF, Bronfort G, Evans R, et al. The efficacy of spinal manipulation, amitriptyline and the combination of both therapies for the prophylaxis of migraine headache. J Manipulative Physiol Ther. 1998 Oct;21(8):511-9. PMID 9798179.
166. Mathew NT. Prophylaxis of migraine and mixed headache. A randomized controlled study. Headache. 1981 May;21(3):105-9. PMID 7021472.
167. Holroyd KA, Cottrell CK, O'Donnell FJ, et al. Effect of preventive (beta blocker) treatment, behavioural migraine management, or their combination on outcomes of optimised acute treatment in frequent migraine: randomised controlled trial. BMJ. 2010;341:c4871. PMID 20880898.
168. Seng EK, Holroyd KA. Dynamics of changes in self-efficacy and locus of control expectancies in the behavioral and drug treatment of severe migraine. Annals of behavioral medicine : a publication of the Society of Behavioral Medicine; 2010. p. 235-47.
169. Elkind AH, O'Carroll P, Blumenfeld A, et al. A series of three sequential, randomized, controlled studies of repeated treatments with botulinum toxin type A for migraine prophylaxis. J Pain. 2006 Oct;7(10):688-96. PMID 17018329.
170. Silberstein SD, Stark SR, Lucas SM, et al. Botulinum toxin type A for the prophylactic treatment of chronic daily headache: a randomized, double-blind, placebo-controlled trial. Mayo Clin Proc. 2005 Sep;80(9):1126-37. PMID 16178492.
171. Stensrud P, Sjaastad O. Short-term clinical trial of phopranolol in racemic form (Inderal), D-propranolol and placebo in migraine. Acta neurologica Scandinavica; 1976. p. 229-32.
172. Carroll JD, Reidy M, Savundra PA, et al. Long-acting propranolol in the prophylaxis of migraine: a comparative study of two doses. Cephalalgia. 1990 Apr;10(2):101-5. PMID 2193712.
173. Havanka-Kanniainen H, Hokkanen E, Myllyla VV. Long acting propranolol in the prophylaxis of migraine. Comparison of the daily doses of 80 mg and 160 mg. Headache; 1988. p. 607-11.
174. al-Qassab HK, Findley LJ. Comparison of propranolol LA 80 mg and propranolol LA 160 mg in migraine prophylaxis: a placebo controlled study. Cephalalgia. 1993 Apr;13(2):128-31. PMID 8495455.
175. Ekbom K, Lundberg PO. Clinical trial of LB-46 (d, 1-4-(2-hydroxy-3-isopropylaminopropoxy)indol. An adrenergic beta-receptor blocking agent in migraine prophylaxis. Headache; 1972. p. 15-7.
176. Ryan R, Ryan R, Sudilovsky A. Nadolol and placebo comparison study in the prophylactic treatment of migraine. Panminerva Med; 1982. p. 89-94.
177. Ryan R, Ryan R, Sudilovsky A. Nadolol: Its use in the prophylactic treatment of migraine. Headache; 1983. p. 26-31.
178. van de Ven LL, Franke CL, Koehler PJ. Prophylactic treatment of migraine with bisoprolol: a placebo-controlled study. Cephalalgia. 1997 Aug;17(5):596-9. PMID 9251876.

179. Lampl C, Huber G, Adl J, et al. Two different doses of amitriptyline ER in the prophylaxis of migraine: long-term results and predictive factors. Eur J Neurol. 2009 Aug;16(8):943-8. PMID 19456855.
180. Lemstra M, Stewart B, Olszynski WP. Effectiveness of multidisciplinary intervention in the treatment of migraine: a randomized clinical trial. Headache. 2002 Oct;42(9):845-54. PMID 12390609.
181. Matchar DB, Harpole L, Samsa GP, et al. The headache management trial: a randomized study of coordinated care. Headache. 2008 Oct;48(9):1294-310. PMID 18547268.
182. Fritsche G, Frettlöh J, Hüppe M, et al. Prevention of medication overuse in patients with migraine. Pain; 2010. p. 404-13.
183. Rothrock JF, Parada VA, Sims C, et al. The impact of intensive patient education on clinical outcome in a clinic-based migraine population. Headache. 2006 May;46(5):726-31. PMID 16643574.
184. Hoffmann W, Herzog B, Muhlig S, et al. Pharmaceutical care for migraine and headache patients: a community-based, randomized intervention. Ann Pharmacother. 2008 Dec;42(12):1804-13. PMID 19001531.
185. Sondergaard J, Foged A, Kragstrup J, et al. Intensive community pharmacy intervention had little impact on triptan consumption: a randomized controlled trial. Scand J Prim Health Care. 2006 Mar;24(1):16-21. PMID 16464810.
186. Bussone G, Diener HC, Pfeil J, et al. Topiramate 100 mg/day in migraine prevention: a pooled analysis of double-blind randomised controlled trials. Int J Clin Pract. 2005 Aug;59(8):961-8. PMID 16033621.
187. Silberstein S, Lipton R, Dodick D, et al. Topiramate treatment of chronic migraine: a randomized, placebo-controlled trial of quality of life and other efficacy measures. Headache. 2009 Sep;49(8):1153-62. PMID 19719543.
188. Brandes JL, Saper JR, Diamond M, et al. Topiramate for migraine prevention: a randomized controlled trial. JAMA. 2004 Feb 25;291(8):965-73. PMID 14982912.
189. Mei D, Capuano A, Vollono C, et al. Topiramate in migraine prophylaxis: a randomised double-blind versus placebo study. Neurol Sci. 2004 Dec;25(5):245-50. PMID 15624081.
190. Silberstein SD, Neto W, Schmitt J, et al. Topiramate in migraine prevention: results of a large controlled trial. Arch Neurol. 2004 Apr;61(4):490-5. PMID 15096395.
191. Silberstein S. Efficacy and safety of topiramate in migraine prevention: a dose-ranging, placebo-controlled, double-blind, multicenter study. Advanced Studies in Medicine. 2003;3(6C):S565-8.
192. Edwards KR, Potter DL, Wu SC, et al. Topiramate in the preventive treatment of episodic migraine: a combined analysis from pilot, double-blind, placebo-controlled trials. CNS Spectr. 2003 Jun;8(6):428-32. PMID 12858132.
193. Freitag FG, Forde G, Neto W, et al. Analysis of pooled data from two pivotal controlled trials on the efficacy of topiramate in the prevention of migraine. J Am Osteopath Assoc. 2007 Jul;107(7):251-8. PMID 17682112.
194. Diamond S, Medina JL. Double blind study of propranolol for migraine prophylaxis. Headache; 1976. p. 24-7.
195. Weber RB, Reinmuth OM. The treatment of migraine with propranolol. Neurology; 1972. p. 366-9.
196. Briggs RS, Millac PA. Timolol in migraine prophylaxis. Headache. 1979 Nov;19(7):379-81. PMID 511540.
197. Vahedi K, Taupin P, Djomby R, et al. Efficacy and tolerability of acetazolamide in migraine prophylaxis: a randomised placebo-controlled trial. J Neurol. 2002 Feb;249(2):206-11. PMID 11985388.
198. Rompel H, Bauermeister PW. Aetiology of migraine and prevention with carbamazepine (Tegretol): results of a double-blind, cross-over study. S Afr Med J. 1970 Jan 24;44(4):75-80. PMID 4905910.
199. Mathew NT, Rapoport A, Saper J, et al. Efficacy of gabapentin in migraine prophylaxis. Headache. 2001 Feb;41(2):119-28. PMID 11251695.
200. Wessely P, Baumgartner C, Klingler D, et al. Preliminary results of a double-blind study with the new migraine prophylactic drug Gabapentin. Cephalalgia; 1987. p. 477-8.
201. Silberstein S, Saper J, Berenson F, et al. Oxcarbazepine in migraine headache: a double-blind, randomized, placebo-controlled study. Neurology. 2008 Feb 12;70(7):548-55. PMID 18268247.
202. Forssman B, Lindblad CJ, Zbornikova V. Atenolol for migraine prophylaxis. Headache; 1983. p. 188-90.
203. Schachtel BP, Thoden WR. Onset of action of ibuprofen in the treatment of muscle-contraction headache. Headache. 1988 Aug;28(7):471-4. PMID 3072316.

204. Couch JR, Hassanein RS. Amitriptyline in migraine prophylaxis. Arch Neurol. 1979 Nov;36(11):695-9. PMID 508127.
205. Herrmann WM, Horowski R, Dannehl K, et al. Clinical effectiveness of lisuride hydrogen maleate: a double-blind trial versus methysergide. Headache. 1977 May;17(2):54-60. PMID 324950.
206. Diamond S, Solomon GD, Freitag FG, et al. Fenoprofen in the prophylaxis of migraine: a double-blind, placebo controlled study. Headache; 1987. p. 246-9.
207. Solomon GD, Kunkel RS. Flurbiprofen in the prophylaxis of migraine. Cleve Clin J Med. 1993 Jan-Feb;60(1):43-8. PMID 8443934.
208. Anthony M, Lance JW. Indomethacin in migraine. Med J Aust. 1968 Jan 13;1(2):56-7. PMID 4867513.
209. Masel BE, Chesson AL, Peters BH, et al. Platelet antagonists in migraine prophylaxis. A clinical trial using aspirin and dipyridamole. Headache; 1980. p. 13-8.
210. Adelman J, Freitag FG, Lainez M, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. Pain Med. 2008 Mar;9(2):175-85. PMID 18298700.
211. Steiner TJ, Findley LJ, Yuen AW. Lamotrigine versus placebo in the prophylaxis of migraine with and without aura. Cephalalgia. 1997 Apr;17(2):109-12. PMID 9137848.
212. Johannsson V, Nilsson LR, Widelius T, et al. Atenolol in migraine prophylaxis: a double-blind cross-over multicenter study. Headache; 1987. p. 372-4.
213. Somerville BW, Herrmann WM. Migraine prophylaxis with lisuride. A double blind study of lisuride versus placebo. Headache; 1976. p. 85-6.
214. Whewell J. Methysergide in prophylaxis of migraine: a clinical trial in general practice. Br Med J. 1966 Aug 13;2(5510):394-5. PMID 5331176.
215. McArthur JC, Marek K, Pestronk A, et al. Nifedipine in the prophylaxis of classic migraine: a crossover, double-masked, placebo-controlled study of headache frequency and side effects. Neurology; 1989. p. 284-6.
216. (MINES) M-NESG. European multicenter trial of nimodipine in the prophylaxis of classic migraine (migraine with aura). Headache. 1989 Nov;29(10):639-42. PMID 2693406.
217. Welch KMA, Ellis DJ, and Keenan PA. Successful migraine prohpylaxis with naproxen sodium. Neurology; 1985.
218. Mikkelsen BM, Falk JV. Prophylactic treatment of migraine with tolfenamic acid. A comparative double-blind crossover study between tolfenamic acid and placebo. Acta neurologica Scandinavica; 1982. p. 105-11.
219. Keskinbora K, Aydinli I. A double-blind randomized controlled trial of topiramate and amitriptyline either alone or in combination for the prevention of migraine. Clin Neurol Neurosurg. 2008 Dec;110(10):979-84. PMID 18620801.
220. Shaygannejad V, Janghorbani M, Ghorbani A, et al. Comparison of the effect of topiramate and sodium valporate in migraine prevention: a randomized blinded crossover study. Headache. 2006 Apr;46(4):642-8. PMID 16643559.
221. Baldrati A, Cortelli P, Procaccianti G, et al. Propranolol and acetylsalicylic acid in migraine prophylaxis. Double-blind crossover study. Acta Neurol Scand; 1983. p. 181-6.
222. Langohr HD, Gerber WD, Koletzki E, et al. Clomipramine and metoprolol in migraine prophylaxis--a double-blind crossover study. Headache. 1985 Mar;25(2):107-13. PMID 3886599.
223. Saper JR, Mathew NT, Loder EW, et al. A double-blind, randomized, placebo-controlled comparison of botulinum toxin type a injection sites and doses in the prevention of episodic migraine. Pain Med. 2007 Sep;8(6):478-85. PMID 17716321.
224. Petri S, Tolle T, Straube A, et al. Botulinum toxin as preventive treatment for migraine: a randomized double-blind study. Eur Neurol. 2009;62(4):204-11. PMID 19622887.
225. Aurora SK, Dodick DW, Turkel CC, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. Cephalalgia. 2010 Jul;30(7):793-803. PMID 20647170.
226. Diener HC, Dodick DW, Aurora SK, et al. OnabotulinumtoxinA for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. Cephalalgia. 2010 Jul;30(7):804-14. PMID 20647171.
227. Aurora SK, Gawel M, Brandes JL, et al. Botulinum toxin type a prophylactic treatment of episodic migraine: a randomized, double-blind, placebo-controlled exploratory study. Headache. 2007 Apr;47(4):486-99. PMID 17445098.

228. Silberstein SD, Lipton RB, Dodick DW, et al. Efficacy and safety of topiramate for the treatment of chronic migraine: a randomized, double-blind, placebo-controlled trial. Headache. 2007 Feb;47(2):170-80. PMID 17300356.
229. Lipton RB, Silberstein S, Dodick D, et al. Topiramate intervention to prevent transformation of episodic migraine: the topiramate INTREPID study. Cephalalgia. 2011 Jan;31(1):18-30. PMID 20974598.
230. Mei D, Ferraro D, Zelano G, et al. Topiramate and triptans revert chronic migraine with medication overuse to episodic migraine. Clin Neuropharmacol. 2006 Sep-Oct;29(5):269-75. PMID 16960472.
231. Silberstein SD, Loder E, Forde G, et al. The impact of migraine on daily activities: effect of topiramate compared with placebo. Curr Med Res Opin. 2006 Jun;22(6):1021-9. PMID 16846536.
232. Storey JR, Calder CS, Hart DE, et al. Topiramate in migraine prevention: a double-blind, placebo-controlled study. Headache. 2001 Nov-Dec;41(10):968-75. PMID 11903524.
233. Couch JR. Amitriptyline in the prophylactic treatment of migraine and chronic daily headache. Headache. 2011 Jan;51(1):33-51. PMID 21070231.
234. Orholm M, Honore PF, Zeeberg I. A randomized general practice group-comparative study of femoxetine and placebo in the prophylaxis of migraine. Acta Neurol Scand. 1986 Sep;74(3):235-9. PMID 3538753.
235. Steiner TJ, Ahmed F, Findley LJ, et al. S-fluoxetine in the prophylaxis of migraine: a phase II double-blind randomized placebo-controlled study. Cephalalgia. 1998 Jun;18(5):283-6. PMID 9673809.
236. Dodick DW, Mauskop A, Elkind AH, et al. Botulinum toxin type a for the prophylaxis of chronic daily headache: subgroup analysis of patients not receiving other prophylactic medications: a randomized double-blind, placebo-controlled study. Headache. 2005 Apr;45(4):315-24. PMID 15836567.
237. Relja M, Poole AC, Schoenen J, et al. A multicentre, double-blind, randomized, placebo-controlled, parallel group study of multiple treatments of botulinum toxin type A (BoNTA) for the prophylaxis of episodic migraine headaches. Cephalalgia. 2007 Jun;27(6):492-503. PMID 17428299.
238. Di Trapani G, Mei D, Marra C, et al. Gabapentin in the prophylaxis of migraine: a double-blind randomized placebo-controlled study. Clin Ter. 2000 May-Jun;151(3):145-8. PMID 10958046.
239. Meyer JS, Hardenberg J. Clinical effectiveness of calcium entry blockers in prophylactic treatment of migraine and cluster headaches. Headache; 1983. p. 266-77.
240. Barden J, Derry S, McQuay HJ, et al. Bias from industry trial funding? A framework, a suggested approach, and a negative result. Pain. 2006 Apr;121(3):207-18. PMID 16495012.
241. Fox AW. Disease modification in migraine: study design and sample size implications. Headache. 2008 Sep;48(8):1169-75. PMID 18819175.
242. Arends LR, Hoes AW, Lubsen J, et al. Baseline risk as predictor of treatment benefit: three clinical = meta-re-analyses. Stat Med. 2000;19:3497-518.
243. Hazard E, Munakata J, Bigal ME, et al. The burden of migraine in the United States: current and emerging perspectives on disease management and economic analysis. Value in Health. 2009 Jan;12(1):55-64. PMID 18671771.
244. Russell MB, Hilden J, Sorensen SA, et al. Familial occurrence of migraine without aura and migraine with aura. Neurology. 1993 Jul;43(7):1369-73. PMID 8392151.
245. Gentile G, Missori S, Borro M, et al. Frequencies of genetic polymorphisms related to triptans metabolism in chronic migraine. Journal of Headache & Pain. 2010 Apr;11(2):151-6. PMID 20213484.
246. Schurks M, Zee RY, Buring JE, et al. ACE D/I polymorphism, migraine, and cardiovascular disease in women. Neurology. 2009 Feb 17;72(7):650-6. PMID 19221299.
247. Feldman HL. Pushing drugs: genomics and genetics, the pharmaceutical industry, and the law of negligence. Washburn Law Journal. 2003;42(3):575-99. PMID 15115000.
248. Antonaci F, Chimento P, Diener H-C, et al. Lessons from placebo effects in migraine treatment. Journal of Headache & Pain. 2007 Feb;8(1):63-6. PMID 17361384.
249. Bingham MF, Johnson FR, Miller D. Modeling choice behavior for new pharmaceutical products. Value in Health. 2001 Jan-Feb;4(1):32-44. PMID 11704970.

250. Etemad LR, Yang W, Globe D, et al. Costs and utilization of triptan users who receive drug prophylaxis for migraine versus triptan users who do not receive drug prophylaxis. Journal of Managed Care Pharmacy. 2005 Mar;11(2):137-44. PMID 15766320.
251. Radley DC, Finkelstein SN, Stafford RS. Off-label prescribing among office-based physicians. Arch Intern Med. 2006 May 8;166(9):1021-6. PMID 16682577.
252. Edwards IR. Off-label pharmacovigilance. Drug Safety. 2011 Oct 1;34(10):795-7. PMID 21879775.
253. Layton D, Hazell L, Shakir SA. Modified prescription-event monitoring studies: a tool for pharmacovigilance and risk management. Drug Safety. 2011 Dec 1;34(12):e1-9. PMID 22077508.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
CI	Confidence interval
FDA	Food and Drug Administration
MeSH	Medical Subject Heading
PICOTS	Population, Intervention, Comparator, Outcome, Timing, and Setting
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	Randomized controlled trial
VAS	Visual analog scale

Part B. Preventive Pharmacological Treatments for Migraine in Children

Structured Abstract

Objectives: To assess comparative effectiveness and safety of preventive pharmacological treatments for community-dwelling children with episodic or chronic migraine.

Data Sources: We searched major electronic bibliographic databases, including Medline and Cochrane Central Register of Controlled Trials, and trial registries up to March 29, 2012.

Review Methods: We performed a systematic review of randomized trials published in English that examined episodic or chronic migraine and rates of complete cessation of or reduction of monthly migraine frequency by ≥50 percent, reduction in migraine-related disability, and improvement in quality of life with off-label drugs (no preventive drugs were approved in children). Studies that compared drugs with nonpharmacological interventions and drug management interventions were also eligible. We calculated absolute risk differences and pooled them with random-effects models, and calculated numbers of outcome events attributable-to-treatment effects per 1,000 treated.

Results: Episodic migraine prevention in children was examined in 22 publications of 21 RCTs that enrolled 1,853 children and in 40 nonrandomized studies. Individual RCTs offered low strength of evidence due to risk of bias and imprecision. Propranolol resulted in complete cessation of migraine attacks in 713 per 1,000 children treated (95 percent CI, 452 to 974) (one RCT). Trazodone (one RCT) and nimodipine (one RCT) decreased migraine days more effectively than placebo. Topiramate (moderate strength of evidence from two RCTs), divalproex (two RCTs), and clonidine (one RCT) were no more effective than placebo in preventing migraine. Sodium valproate versus propranolol (two RCTs) or topiramate (one RCT) demonstrated no significant differences in migraine prevention or migraine-related disability. Metoprolol tended to be less effective than stress management in preventing migraine or reducing migraine severity (one RCT). Propranolol was less effective than self-hypnosis on absolute number of migraine attacks (one RCT). Multidisciplinary drug management was more effective than usual care in preventing migraine in children and adolescents (one RCT), but the effect did not sustain at 6 months of followup. Topiramate (pooled four RCTs) and divalproex sodium (two RCTs) resulted in treatment discontinuation due to adverse effects more often than placebo. Treatment discontinuation due to adverse effects did not differ between trazodone (one RCT), propranolol (one RCT), clonidine (one RCT), and placebo. No RCTs examined prevention of chronic migraine in children.

Conclusions: Limited low strength evidence suggested that propranolol was more effective than placebo for preventing migraine in children, with no bothersome adverse effects that could lead to treatment discontinuation. Long-term preventive benefits are unknown both for drugs and nonpharmacological interventions. No studies examined quality of life or provided evidence for individualized treatment decisions. Future research is needed for identifying effective and safe treatments to prevent episodic and chronic migraine in children.

Contents

Executive Summary ES-1
Introduction 1
Key Questions 2
Methods 4
Search Strategy 4
Eligibility 4
Inclusion Criteria 4
Exclusion Criteria 5
Risk of Bias Assessment 6
Grading the Evidence for Each Key Question 6
Assessing Applicability 7
Data Extraction 7
Data Synthesis 8
Results 9
Study Overview 9
Characteristics 9
Risk of Bias 10
Adverse Effects with Antiepileptic Drugs 14
Antidepressants 15
Beta Blockers 15
Antiadrenergic Drugs 15
Magnesium Oxide 15
Botulinum Toxin 15
Comparative Safety of Topiramate Versus Sodium Valproate 16
Duscussion 22
Key Messages 23
References 28
Abbreviations 33

Tables

Table 1. Criteria to Rank Strength of Evidence 7
Table 2. Migraine Prevention in Children 17
Table 3. Evidence of Treatment Discontinuation Due to Adverse Effects with Migraine Preventive Drugs Versus Placebo in Children 19
Table 4. Treatment of Discontinuation Due to Adverse Effects with Migraine Preventive Drugs Versus Placebo in Children 20
Table 5. Adverse Effects with Antiepileptic Drugs for Migraine Prevention in Children 21
Table 6. Evidence of Migraine Prevention in Children 25
Table 7. Future Research Needs 26

Figures

Figure 1. Analytical Framework 5
Figure 2. Study Flow 9

Appendixes

Appendix A. Search Strings
Appendix B. Ongoing Studies of Migraine Prevention in Children
Appendix C. Analytical Framework
Appendix D. Evidence Tables
Appendix E. Excluded Studies

Executive Summary

Introduction

This review of migraine prevention is presented in two parallel reports, one focusing on children and one on adults. Here we address migraine prevention in children 6 to 18 years old.

According to the International Classification of Headache Disorders (ICHDII), migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours.[1, 2] Migraine headaches range from moderate to very severe[3] and are sometimes debilitating.[4] In the United States, migraine affects 5 percent of boys[5, 6] and 7.7 percent of girls.[7, 8] Childhood migraine is more prevalent in lower income families.[7] Among adolescents, migraine is more prevalent in whites than African Americans.[7]

Migraine frequency is classified as either episodic or chronic[2] according to the number of monthly headache days, with episodic being ≤15 days, and chronic being ≥15 days. Sometimes migraine may be described as chronic simply because the attacks recur over long periods of time. Chronic migraine affects 2 percent of children and adolescents.[9]

All migraine types significantly affect children's physical, psychological, and social well-being, and can impose serious lifestyle restrictions.[9] Indeed, the majority of adolescents with chronic migraine have some related disability.[9] Yet, according to the Chronic Daily Headache in Adolescents Study (C-dAS), fewer than half of adolescents with chronic migraine had visited a healthcare provider, and fewer than one in five had taken medications to prevent headaches during the previous month.[9] Approximately 31 percent of children with migraine had missed at least 1 day of school in the previous 3 months because of the condition,[10] which overall has been shown to impair learning and school productivity by ≥50 percent.[10]

Many children with frequent or severe attacks need treatment, which falls into two categories: (1) treatment for acute attacks, and (2) migraine prevention. Our review focuses on preventive treatments for childhood migraine.[11, 12] The Food and Drug Administration has approved no drugs for migraine prevention in children; therefore, pediatricians prescribe either drugs approved for adults or off-label drugs (approved for clinical conditions other than migraine prevention).[13, 14] These drug classes cause common and serious adverse effects, including metabolic and hormonal abnormalities.[15-19] Migraine preventive drug choices are based on efficacy and safety of approved and off-label drugs.[20-27]

Preventive treatment aims to eliminate headache pain.[20, 21, 28] Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of ≥50 percent after 3 months.[3] In addition to pain relief, preventive drugs can also decrease severity of migraine attacks and reduce restrictions in daily activities and schooling.[29, 30]

Our review focuses on the comparative effectiveness and safety of drugs for preventing migraine attacks in children in ambulatory care settings; our results may help inform treatment recommendations.

After discussions with key informants and the Technical Expert Panel,[31] we formulated a list of eligible pharmacological classes. We specifically opted not to synthesize studies of flunarizine because the FDA has not approved it. We conducted a comprehensive literature review following the principles in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program[32, 33] and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews (registration number CRD42011001858).[34]

Key Questions

Key Question 1

What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children?

f. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
g. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
h. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
i. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
j. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Key Question 2

What are the comparative harms from pharmacological treatments for preventing migraine attacks in children?

d. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
e. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?
f. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) improve safety of the treatments?

Key Question 3

Which characteristics of children predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks?

Methods

Search Strategy

We used the standard methods developed by the AHRQ EPC program.[32, 33] We searched several bibliographic databases, including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, SCIRUS, the FDA Web site, clinical trial registries, and reference lists of published reviews to find ongoing, completed, and published trials of migraine prevention in children.

Eligibility

Three investigators independently determined study eligibility.[35, 36] We defined the target population as community-dwelling children with episodic migraine, chronic daily headache, or chronic migraine defined according to criteria set by the International Headache Society.[22] We formulated a list of eligible interventions after discussions with key informants and technical experts, and after consideration of public comments. To assess benefits, we included randomized controlled trials (RCTs) published in English up to March 29, 2012. We defined eligible intermediate and patient-centered outcomes as listed in the analytical framework (Figure 1 in the full report). We reviewed original clinical studies that included children with migraine, comorbid headache disorders, or tension headache as long as migraine prevention was examined. To assess harms of treatments we included published and unpublished evidence of the adverse effects of drugs in children with migraine.[35, 37] We defined harms as the totality of all possible adverse consequences of an intervention.[37] We analyzed harms regardless of how authors perceived the causality of treatments.

We excluded studies of treatments aimed at acute migraine attacks, studies that involved patients with migraine variants (such as basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine), and patients who were hospitalized or in emergency rooms.[2, 38, 39] We also excluded hemiplegic migraine, a pathophysiologically distinct disorder with its own classification.[39] We excluded studies that included some pediatric patients with migraine without separately reporting those outcomes, studies that involved surgical treatments for migraine; preclinical pharmacokinetic studies of eligible drugs, studies that examined the pathophysiology of migraine and reported instrumental measurements or biochemical outcomes, studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk), and studies that examined eligible drugs on populations with other diseases. Studies evaluating the efficacy of nonpharmacological treatments or economic outcomes were beyond the scope of this review.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies according to study design[36] using criteria from the Cochrane tool for bias in interventional studies:[40]

1. Random allocation of the subjects to treatment groups.
2. Masking of the treatment status.
3. Adequacy of allocation concealment.
4. Adequacy of randomization according to baseline similarity of the subjects in treatment groups by demographics, migraine frequency and severity, and response to previous treatments.
5. Intention-to-treat principles.
6. Selective outcome reporting when compared to the posted protocols (when trials were registered) or methods section in the articles.

We assumed a low risk of bias when RCTs met all the risk of bias criteria, a moderate risk of bias if at least one of the risk of bias criteria was not met, and a high risk of bias if two or more risk of bias criteria were not met. We concluded an unknown risk of bias for studies with poorly reported risk of bias criteria. Masking of treatment status was not feasible for RCTs that examined nondrug therapies as comparators. We evaluated risk of bias in such RCTs using the

four other criteria described above. We appraised risk of bias in nonrandomized studies according to selection, attrition, and detection biases.[41]

Since all outcomes in the review are self-reported, masking of outcome assessment was not essential in evaluating risk of bias, but masking of treatment was. We evaluated disclosure of conflict of interest by the authors of individual studies and funding sources but did not use this information to downgrade quality of individual studies.

Grading the Evidence for Each Key Question

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome and assessed treatment discontinuation due to harms.[42] When evidence was available, we also included dose-response association, strength of association, and reporting bias. We evaluated the strength of the association, defining *a priori* a large effect when relative risk is >2 and a very large effect when relative risk is >5.[36] We defined low magnitude of effect when the relative risk was significant but <2. We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95 percent CIs, and pooled sample had ≥400 events.[43] We did not include justification of the sample size into grading of the evidence nor did we conduct *post hoc* statistical power analysis. We defined reporting bias as publication bias, selective outcomes reporting, and multiple publication bias. We did not perform formal statistical tests quantifying the biases.[44]

We defined high level of evidence on the basis of consistent findings from well-designed RCTs. We downgraded strength of evidence to moderate if at least one of the four criteria for strength of evidence (risk of bias, directness, consistency, and precision) was not met. We downgraded strength of evidence to low if two or more criteria were not met. We defined evidence as insufficient when a single study with high risk of bias examined treatment effects or associations.

Assessing Applicability

We estimated applicability of the sample by evaluating the selection of children with migraine.[45] Studies of community-dwelling children who received drug treatments with 6 months or more followup had high applicability, as did large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases.

Data Extraction

Researchers used standardized forms to extract data (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041370_1-t_yAjBY2Cn). We conducted a double independent quality control for the data extracted from RCTs; one reviewer abstracted an article and a second reviewer checked the abstracted data for accuracy. We assessed errors by comparing established ranges for each variable and data charts from the original articles. Any detected discrepancies were discussed. We abstracted the information relevant to the PICOTS framework. We abstracted minimum datasets to reproduce the results presented by the authors. For categorical variables we abstracted the number of events among treatment groups to calculate rates, relative risk, and absolute risk differences. Means and standard deviations of continuous variables were abstracted to calculate mean differences with a 95 percent confidence interval (CI).

For RCTs in the quantitative analysis set we abstracted the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We abstracted the time when the outcomes were assessed as weeks from randomization and time of followup after treatments.

We abstracted inclusion and exclusion criteria, drug regimen and doses, and patient characteristics that can modify treatment effects, including demographics, migraine definition, baseline frequency, severity, and prior treatment status. We abstracted sponsorship of the studies and conflict of interest by the authors.

Data Synthesis

We summarized the results into evidence tables. We focused on patient-centered outcomes, such as reduction in migraine attack rate by ≥50 percent from baseline, quality of life, patient satisfaction, and composite outcomes that included migraine frequency and severity. We incorporated risk of bias in individual studies into the synthesis of evidence by using individual risk of bias criteria rather than a global score or a ranking category of overall risk of bias.[46, 47]

Using Meta-Analyst[48] and STATA®[49] software at a 95 percent CI, we calculated the relative risk and absolute risk difference from the abstracted events and the mean differences in continuous variables from the reported means and standard deviations.

Pooling criteria for Key Questions 1 and 2 included the same active drug treatments and comparators and the same definitions of the outcomes. Standardized mean differences were calculated for different continuous measures of the same outcome. We did not pool RCTs with nonrandomized studies or studies of different pharmacological drug classes with each other.

We tested consistency in the results by comparing the direction and strength of the association[42] and assessed heterogeneity in results with Chi-square and I-square tests.[50, 51] Using the random effects model, we incorporated into the pooled analysis any differences between trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[52]

The number needed to treat to achieve one event of a patient-centered outcome was calculated as the reciprocal of statistically significant absolute risk differences (ARD) in rates of outcome events in the active and control groups.[49, 53] We calculated means and 95 percent CIs for the number needed to treat as reciprocal of pooled ARD when ARD is significant.[54] The number of avoided or excess events (respectively) per population of 1,000 is the difference between the two events rates multiplied by 1,000.

We focused on direct comparisons and synthesized evidence from head-to-head comparative effectiveness studies.

Results

We retrieved 507 references, excluded 349 references, and included 22 references for 21 RCTs and 40 publications of nonrandomized studies (Figure 2 in the full report). Trials aimed to examine prevention of episodic migraine and adverse effects but rarely reported statistical power to detect statistically significant differences in outcomes.

Applicability

The applicability of the enrolled subjects to the target population was good**.** Most trials were conducted in Western countries and recruited children and adolescents in clinics. Only two trials recruited participants from the community. Caucasian girls constituted more than half of all enrolled subjects. Many enrolled subjects were overweight according to their mean age, with

average body mass index being 23±1.6. Children had migraines for an average 3.5 years and suffered from eight migraine attacks per month. Most trials defined migraine according to the International Headache Society diagnostic criteria. Reporting of other characteristics of children was poor. More than half the trials did not report family history of migraine, children's socio-economic status, baseline comorbidity, prior treatments, overuse of drugs for acute migraine, or adherence to assigned treatments. The trials lasted an average 20 weeks (ranging 6 to 52 weeks). Attrition rates averaged 9 percent.

Risk of Bias

We concluded low risk of bias in 50 percent, moderate risk of bias in 25 percent, and unclear risk of bias in 25 percent of all included trials. Most trials were double blinded; however, randomization was adequate in just nine trials. Trials lasted an average of 21 weeks after a run-in period of 5 weeks. We concluded high risk of bias in 40 nonrandomized studies that failed to address selection bias in analyses that provided crude rates of the outcomes.

Key Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children?

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?

Nine randomized placebo-controlled RCTs examined efficacy of drugs for migraine prevention in children.[55-65] The trials included 1,077 children ages 9 to 14. Sample size of RCTs averaged 112.5±109 children, with boys constituting 51 percent. Tables A and B present information on benefits and treatment discontinuation due to adverse effects from included RCTs, strength of evidence, and number of attributable to drug administration events per 1,000 treated children. Table C presents our conclusions about effectiveness and safety of episodic migraine preventive treatments in children. Eligible trials defined clinically important migraine prevention as a complete cessation of migraine attacks and a reduction in monthly migraine frequency by ≥50 or 75 percent.

Off-Label Pharmacological Agents

Antiepileptic Drugs

Topiramate

Topiramate, 100 to 200 mg/day, was no more effective than placebo in reducing monthly migraine attacks by ≥50 percent (two RCTs of 298 children, moderate strength of evidence).[62, 65] Topiramate increased the likelihood of ≥75 percent reduction in migraine days more often than placebo in a single double-blind RCT.[62] Using this statistically significant risk difference, we estimated that 181 children (95 percent CI, 52 to 311) per 1,000 treated experienced a reduction of at least 75 percent in migraine days due to topiramate, 200 mg/day.[62]

Divalproex

Divalproex sodium, 250 to 1,000 mg/day, was no more effective than placebo in reducing monthly migraine attacks by ≥50 percent in one low risk of bias RCT (305 children, low strength of evidence).[63] Divalproex sodium in doses of 250, 500, or 1,000 mg/day was no better than placebo in preventing migraine attacks, decreasing migraine days, or decreasing use of acute drugs.[63, 64]

Antidepressants

Trazodone was more effective than placebo in reducing frequency and duration of migraine attacks by 1.6 per month and at reducing duration of migraine attacks by 8.2 hours per attack (one RCT of 40 children, low strength of evidence).[61]

Beta blockers

Propranolol resulted in a complete cessation of migraine attacks more often than placebo (one RCT of 32 children, low strength of evidence).[55] We estimated that 713 children per 1,000 (95 percent CI, 452 to 974) treated would have no migraine attacks with propranolol.[55]

Antiadrenergic Drugs

Clonidine was no more effective than placebo in preventing migraine, reducing migraine duration or severity, or reducing use of drugs for acute migraine attacks (one RCT of 57 children, low strength of evidence).[56]

Magnesium Oxide

A single RCT demonstrated no significant differences with magnesium oxide and placebo in migraine frequency.[66] Magnesium oxide reduced severity of migraine attacks relative to the placebo group.[66]

b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?

Limited evidence from individual RCTs suggested no differences in migraine prevention with examined drugs, including propranolol, valproate, and topiramate.

Three RCTs examined comparative effectiveness of drugs for migraine prevention in children.[67-69] The trials included 231 children, averaging 9 to 11 years old. The sample size of RCTs averaged 77±38 children; 60 percent of subjects were boys. The trials had moderate[68] or unclear risk of bias.

Two RCTs of 183 children examined comparative effectiveness of sodium valproate versus propranolol and found no significant differences between the drugs for achieving complete cessation of headache attacks or reduction by ≥50 percent from baseline in frequency of migraine attack (low strength of evidence).[67, 68] One RCT of 48 children examined comparative effectiveness of topiramate versus sodium valproate (low strength of evidence) and found no differences in their effects on migraine frequency, intensity, duration, or Pediatric Migraine Disability Assessment Score.[69]

c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?

Limited evidence from individual RCTs suggested that nonpharmacological treatments including self-administered stress management and relaxation techniques more effectively prevented migraine in children than beta blockers. Two small RCTs compared drugs with active nonpharmacological treatments.[58, 70] We concluded unclear risk of bias in both trials because the authors provided insufficient details about methodology.

One RCT of 43 children examined comparative effectiveness of metoprolol versus stress management combined with either progressive relaxation training or cephalic vasomotor feedback and found no significant differences in the percentage of children who improved by ≥50 percent in the headache index (low strength of evidence).[70] In fact, metoprolol tended to less effectively prevent migraine or reduce migraine severity than stress management combined with either progressive relaxation training or cephalic vasomotor feedback.[70]

Comparative effectiveness of propranolol versus nonpharmacological treatments was examined in one RCT of 33 children (low strength of evidence) that found more frequent migraine with the drug than with self-hypnosis.[58]

d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?

No studies compared combined treatments for migraine prevention with drugs alone.

e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Four RCTs published in five articles[63-65, 71, 72] and one pooled analysis of three RCTs[73] examined the dose response effects of preventive antiepileptic drugs in children. All RCTs were double blind with low risk of bias. Higher doses of topiramate (100 to 200 mg/day) [65, 71] or higher doses of divalproex sodium (500 to 1,000 versus 250 mg/day) resulted in no significantly better migraine prevention in a single RCT that examined this association.[63, 64]

e2. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Multidisciplinary drug management, including cognitive-behavioral training, prevented migraine in children and adolescents more effectively than usual care combined with an educational intervention (one RCT of 68 children, low strength of evidence).[74] We estimated that 310 children per 1,000 treated with multimodal cognitive-behavioral training would experience ≥50 percent reduction in migraine frequency (95 percent CI, 70 to 550). The effect, however, did not last at 6 months of followup.[74] Migraine frequency and quality of life did not differ with internet-based self-management versus an education program.[74]

Key Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in children?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?

Topiramate and divalproex sodium resulted in treatment discontinuation due to adverse effects (Table A). Topiramate significantly increased risk of anorexia, weight loss, paresthesia, and upper respiratory tract infection. Antiepileptic drugs had unfavorable safety in contrast with antidepressant trazodone, propranolol, or clonidine. Eleven randomized trials[56, 57, 61-66, 72, 75, 76] and one pooled analysis of three RCTs[73] examined the safety of drugs for migraine prevention in children. The trials included 1,418 children. Sample size averaged 118±94 children, with boys constituting 45 percent of participants. All RCTs were double blind. Based on all risk of bias criteria, we concluded that eight RCTs had low risk of bias and three had moderate risk of bias.[62, 66, 76] Forty nonrandomized studies reported harms with migraine preventive drugs in children.

Adverse Effects with Antiepileptic Drugs

Topiramate

Treatment discontinuation due to adverse effects was greater with topiramate than with placebo in a pooled analysis of four RCTs (low strength of evidence).[62, 65, 72, 73] We estimated that 55 children per 1,000 treated with topiramate would discontinue treatment because of adverse effects.[65, 72] Nonrandomized studies suggested that 19 percent of children discontinued topiramate treatments due to bothersome adverse effects.[77]

A single RCT reported that 260 children per 1,000 treated with topiramate (95 percent CI, 30 to 480) would experience adverse effects.[65] Our pooled analysis of individual adverse effects demonstrated significant increase in risk of anorexia, weight loss, paresthesia, and upper respiratory tract infection with topiramate. We estimated that for every 1,000 children treated with topiramate, 87 would experience unintended weight loss (95 percent CI, 24 to 150), and 105 would be diagnosed with upper respiratory tract infection (95 percent CI, 29 to 182).[62, 65, 73]

Divalproex Sodium

Treatment discontinuation due to adverse effects was greater with 1,000 mg/day but not with 250 mg/day of divalproex sodium in pooled analysis of two RCTs (low level of evidence).[63, 64] The analyses demonstrated that 140 children per 1,000 treated with divalproex sodium would experience adverse effects (95 percent CI, 30 to 250).[63, 64] Nonrandomized studies suggested that 84 percent of children would experience adverse effects with divalproex[78] and 17 percent discontinued treatment due to bothersome adverse effects.[79]

Treatment discontinuation did not differ between the antidepressants trazodone (one RCT),[61] propranolol (one RCT),[76] clonidine (one RCT),[56] and placebo.

b. What are the harms from preventive pharmacologic treatments when compared to pharmacological treatments?

Comparative Safety of Topiramate Versus Sodium Valproate

A single RCT found no differences in adverse effects with topiramate and sodium valproate for 12 weeks in 40 children with migraine.[69]

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) improve safety of the treatments?

We found no studies that examined how drug management can improve safety of migraine preventive medications in children.

Key Question 3. Which characteristics of children predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks?

We found no studies that provided evidence for individualized treatment decisions for migraine prevention in children. No studies examined which characteristics of children might modify effectiveness or safety with preventive drugs.

Discussion

Limited evidence from individual RCTs suggested that only one drug, the beta blocker propranolol, prevented migraine more effectively than placebo (Table B).[80] The antiepileptic drugs clonidine, trazodone, and magnesium oxide failed to prevent migraine in children. Moreover, two other antiepileptic drugs, topiramate and divalproex sodium, both resulted in treatment discontinuation due to adverse effects.

Previously published reviews also reported bothersome adverse effects with antiepileptic drugs in children with migraine[81, 82] or epilepsy.[83] Off-label use of the antidepressant trazodone did not prevent migraine in children. We could not conclude the effectiveness of other antidepressants for preventing migraine in children. Nor could we determine whether adverse effects of antidepressants are similar when used for children with migraine compared to children with depression. We do know that antidepressants may increase risk of suicidal behavior in children and adolescents.[84] Use of off-label psychotropic drugs for migraine prevention could be justified in children with psychiatric comorbidity;[85] however, trials available for review did not report the presence of comorbid illnesses in enrolled patients.

In fact, few available trials examined the seriousness or bothersomeness of harms with drugs. Clinicians considering off-label drugs for children with migraine must therefore base decisions on strong evidence of effectiveness. Few clinical trials followed the recommendations from the Task Force on Adverse Events in Migraine Trials of the International Headache Society[86] when examining the potential harms of these drugs when used in children.

No studies examined specific characteristics of children that may predict the effectiveness or long-term safety of drugs for migraine prevention. Treatment effects may differ between children and adolescents, but published trials did not separately report results for age subgroups.

In head-to-head RCTs, nonpharmacological treatments demonstrated better benefit-to-harm ratios than drugs.[58, 70, 87] Individualized multimodal drug management showed promising results.[74] School-based psychological and drug management have both demonstrated positive results for treating acute headache attacks but have yet to be examined for migraine prevention.[88, 89] RCTs have also yet to examine other drug management interventions, including integrated care, coordinated care, patient education, drug surveillance, and interactive drug monitoring.

Strength of evidence of drug benefits and harms was low in most cases due to risk of bias and imprecise estimates from underpowered RCTs. Reporting quality of trials was poor; few trials

provided detailed information about prior or concomitant treatments, comorbidities, family history, socioeconomic status, acute drug overuse, or other important characteristics of the children studied. On average, the trials lasted 20 weeks and therefore did not provide sufficiently long-term evidence for the benefits and harms of drugs that could be recommended for preventive use over very long periods.

Our review has limitations. We did not synthesize the evidence for flunarizine, a drug shown in RCTs to be effective in preventing migraines in children, because the FDA has not approved this drug. One low risk of bias RCT suggested that flunarizine resulted in ≥50 percent reduction in migraine attacks in 500 children per 1,000 treated (95 percent CI, 260 to 740).[57]

Our comprehensive literature search of several databases, trial registries, and the FDA reviews detected a very low publication rate of registered completed clinical trials involving children. We assumed publication bias, but did not contact the investigators of completed trials for unpublished data. We did request additional data from the sponsors of completed trials, and received few responses. Thus, we know neither the results from unpublished trials, nor how many unregistered studies have been conducted and never published. We relied on reported information and did not contact study authors for additional details about trials (such as design, execution, or poorly reported results we could not reproduce).

Key Messages

Propranolol was more effective than placebo for preventing migraine in children, with no bothersome adverse effects that could lead to treatment discontinuation.

Antiepileptics were no more effective than placebo in preventing migraine but resulted in increased risk of treatment discontinuation due to adverse effects.

Internet-based self-management with multimodal CBT was better than education in preventing migraine in children and adolescents at 6 weeks but not 6 months of followup.

Reporting quality of studies involving children is poor.

Our report offers insights for future research. Future randomized trials should examine comparative effectiveness of multimodal drug and disease management, long-term benefits, safety, and adherence with preventive treatments, and the role of children's characteristics that could modify benefits and harms with preventive drugs. Randomized trials examined few pharmacological agents, while practicing clinicians use many off-label drugs to treat children. Large observational studies, including the American Migraine Prevalence and Prevention study, relied on self-reported use of preventive medications, and did not assess exact drug use or effectiveness.[5] The few available studies of off-label drug use in children show that 5 percent of all prescribed antiepileptic drugs were prescribed for migraine.[90] The National Ambulatory Medical Care Surveys (NAMCS) from 2001 to 2004 demonstrated that 62 percent of outpatient pediatric visits included off-label prescribing; 86 percent of those prescriptions were for pain.[91] European studies demonstrated that about 30 percent of hospitalized children[92] and 40 percent of children in outpatient settings received off-label drug prescriptions.[93] European observational studies found a significantly higher risk of adverse effects with off-label drugs and concluded improper balance of benefits and risks with off-label drugs in pediatric patients.[93, 94]

Little is known about the use of off-label drug utilization for migraine prevention in children or about the comparative effectiveness of the drug classes used. As a first step, these issues should be examined by analyzing administrative databases. Such analyses of Medicaid data could, for example, shed light on practice patterns in migraine prevention and provide insight into the comparative effectiveness of preventive drugs for reducing visits to emergency rooms.

Based on these analyses, RCTs could then be designed to examine the drugs for which benefits and harms ratios were most favorable.

Table A. Effects of preventive pharmacological treatments on reduction in monthly migraine attacks

Outcome	Active	Control	RCTs Reference	Children	Rate active, %	Rate control, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Complete cessation of headache attacks	**Propranolol**	**Placebo**	**1[55]**	**28**	**84.6**	**13.0**	**6.3 (1.7 to 23.5)**	**0.71 (0.45 to 0.97)**	**1 (1 to 2)**	**713 (452 to 974)**	**Low**
	Clonidine	Placebo	1[56]	57	10.7	24.1	0.4 (0.1 to 1.5)	-0.13 (-0.33 to 0.06)			Low
	Sodium valproate	Propranolol	2[67, 68]	183	17.1	15.4	1.2 (0.6 to 2.2)	0.02 (-0.09 to 0.12)			Low
Reduction by 50% in migraine attack frequency	Topiramate	Placebo	2[62, 65]	298	58.2	45.7	1.3 (0.9 to 1.8)	0.15 (-0.06 to 0.37)			Moderate
	Divalproex sodium	Placebo	1[63]	305	49.0	45.0	1.1 (0.8 to 1.5)	0.04 (-0.12 to 0.20)			Low
	Propranolol	Placebo	1[55]	28	7.7	0.0	3.4 (0.2 to 77.6)	0.08 (-0.11 to 0.26)			Low
	Clonidine	Placebo	1[56]	57	32.1	27.6	1.2 (0.5 to 2.6)	0.05 (-0.19 to 0.28)			Low
	Sodium valproate	Propranolol	2[67]	183	69.5	74.3	0.9 (0.7 to 1.2)	-0.07 (-0.30 to 0.15)			Low
	Metoprolol	**Progressive relaxation training + stress management**	**1[70]**	**28**	**38.5**	**80.0**	**0.5 (0.2 to 1.0)**	**-0.42 (-0.75 to -0.08)**	**-2 (-12 to -1)**	**-415 (-748 to -82)**	**Low**
	Metoprolol	Cephalic vasomotor feedback + stress management	1[70]	28	38.5	53.3	0.7 (0.3 to 1.7)	-0.15 (-0.51 to 0.22)			Low
	Applied relaxation	Educational intervention	1[74]	41	40.9	26.3	1.6 (0.6 to 3.8)	0.15 (-0.14 to 0.43)			Low
	Multimodal cognitive-behavioral training (CBT)	Educational intervention	1[74]	43	29.2	26.3	1.1 (0.4 to 2.9)	0.03 (-0.24 to 0.30)			Low
	Multimodal cognitive-behavioral training (CBT)	Applied relaxation	1[74]	46	29.2	40.9	0.7 (0.3 to 1.6)	-0.12 (-0.39 to 0.16)			Low

Table A. Effects of preventive pharmacological treatments on reduction in monthly migraine attacks (continued)

Outcome	Active	Control	RCTs Reference	Children	Rate active, %	Rate control, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Reduction for need for temporary drug therapy for single attacks	Clonidine	Placebo	1[56]	57	50.0	34.5	1.5 (0.8 to 2.7)	0.16 (-0.10 to 0.41)			Low
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1[69]	48	NA	NA	-0.9 (-5.6 to 3.8)	0.00 (0.00 to 0.00)			Low

Table B. Treatment discontinuation due to adverse effects with migraine preventive drugs versus placebo in children

Drug	RCTs Reference	Children	Rate with drug, %	Rate with placebo, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Divalproex sodium, 1000 mg	**2[63,64]**	**296**	**9.3**	**1.4**	**6.8 (1.6 to 29.5)**	**0.08 (0.03 to 0.13)**	**13 (8 to 34)**	**80 (29 to 130)**	**Low**
Divalproex sodium, 250 mg	2[63,64]	312	2.4	1.4	1.8 (0.3 to 9.5)	0.01 (-0.02 to 0.04)			Low
Divalproex sodium, all doses	2[63,64]	755	4.6	1.4	2.9 (1.0 to 8.3)	0.02 (-0.01 to 0.06)			Low
Topiramate, 100 mg	2[65,72]	136	8.6	3	2.8 (0.6 to 13.5)	0.06 (-0.02 to 0.13)			Low
Topiramate, 50-100 mg	**2[65,72]**	**272**	**8.6**	**3**	**2.8 (0.9 to 8.6)**	**0.06 (0.00 to 0.11)**	**18 (9 to 1000)**	**55 (1 to 110)**	**Low**
Clonidine	1[56]	57	3.5	0	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.13)			Insufficient

Bold - significant differences at 95% confidence level

Table C. Evidence of migraine prevention in children, results from randomized controlled clinical trials

Outcome	Active	Control	RCTs Reference	Conclusion	Strength of Evidence
Complete cessation of headache attacks	Propranolol	Placebo	1[55]	Propranolol was better than placebo in achieving complete cessation of migraine attacks.	Low
	Clonidine	Placebo	1[56]	Clonidine was not better than placebo in achieving complete cessation of migraine attacks.	Low
	Sodium valproate	Propranolol	2[67,68]	Sodium valproate and propranolol had no significant differences in complete cessation of headache attacks.	Low
Reduction by 50% in migraine attack frequency	Topiramate	Placebo	2[62,65]	Topiramate, 100-200 mg/day, did not increase rate of reduction in migraine by 50%.	Moderate
	Divalproex sodium	Placebo	1[63]	Divalproex sodium, 250-100 mg/day did not increase rate of reduction in migraine by 50%.	Low
	Propranolol	Placebo	1[55]	Propranolol did not increase rate of reduction in migraine by 50%.	Low
	Clonidine	Placebo	1[56]	Clonidine did not increase rate of reduction in migraine by 50%.	Low
Reduction in frequency of migraine attack by ≥50% from baseline	Sodium valproate	Propranolol	2[67,68]	Sodium valproate and propranolol had no significant differences in reduction of migraine attack by ≥50% from baseline with both drugs.	Low
Reduction by ≥50% in migraine attack frequency	Metoprolol	Cephalic vasomotor feedback +stress management	1[70]	Metoprolol and cephalic vasomotor feedback + stress management had no significant differences in reduction of migraine attacks by ≥50%.	Low
	Applied relaxation	Educational intervention	1[74]	Applied relaxation and educational intervention had no significant differences in reduction of migraine attacks by ≥50%.	Low
	Multimodal cognitive-behavioral training (CBT)	Educational intervention	1[74]	Multimodal CBT was better than Educational intervention at 6 weeks but not 6 month in reduction of migraine attacks by ≥50%.	Low
	Multimodal CBT	Applied relaxation	1[74]	Multimodal CBT and applied relaxation had no significant differences in reduction of migraine attacks by ≥50%.	Low
Reduction in drug therapy for acute attacks	Clonidine	Placebo	1[56]	Clonidine did not decrease drug utilization for acute migraine attacks.	Low
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1[69]	Topiramate and sodium valproate had no significant differences in Pediatric Migraine Disability Assessment Score.	Low

Glossary

AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
C-dAS	Chronic Daily Headache in Adolescents Study
CBT	Cognitive behavioral training
CI	Confidence interval
NAMCS	National Ambulatory Medical Care Surveys
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCTs	Randomized controlled trials

References

1. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
2. Silberstein SD. Preventive migraine treatment. Neurol Clin. 2009 May;27(2):429-43. PMID 19289224.
3. Solomon GD, Santanello N. Impact of migraine and migraine therapy on productivity and quality of life. Neurology. 2000;55(9 Suppl 2):S29-35. PMID 11089517.
4. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007 Mar;47(3):355-63. PMID 17371352.
5. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002 Mar 26;58(6):885-94. PMID 11914403.
6. Bigal ME, Lipton RB, Winner P, et al. Migraine in adolescents: association with socioeconomic status and family history. Neurology. 2007 Jul 3;69(1):16-25. PMID 17606878.
7. Hernandez-Latorre MA, Roig M. Natural history of migraine in childhood. Cephalalgia. 2000 Jul;20(6):573-9. PMID 11075841.
8. Lipton RB, Manack A, Ricci JA, et al. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). Headache. 2011 May;51(5):693-706. PMID 21521206.
9. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001 Jul-Aug;41(7):646-57. PMID 11554952.
10. Sprenger T, Goadsby PJ. Migraine pathogenesis and state of pharmacological treatment options. BMC Medicine. 2009;7:71. PMID 19917094.
11. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. Curr Opin Neurol. 2006 Jun;19(3):294-8. PMID 16702838.
12. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. Neurol Sci. 2008 May;29 Suppl 1:S110-22. PMID 18545911.
13. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427-9. PMID 18385495.
14. Fraguas D, Merchan-Naranjo J, Laita P, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. Journal of Clinical Psychiatry. 2008 Jul;69(7):1166-75. PMID 18588363.
15. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2006 Jul;45(7):771-91. PMID 16832314.
16. Pappagallo M, Silva R. The effect of atypical antipsychotic agents on prolactin levels in children and adolescents. J Child Adolesc Psychopharmacol. 2004 Fall;14(3):359-71. PMID 15650493.
17. Kumra S, Oberstar JV, Sikich L, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizophr Bull. 2008 Jan;34(1):60-71. PMID 17923452.
18. Dubois D. Toxicology and overdose of atypical antipsychotic medications in children: does newer necessarily mean safer? Curr Opin Pediatr. 2005 Apr;17(2):227-33. PMID 15800418.

19. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008 May;28(5):484-95. PMID 18294250.
20. Schroeder BM. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. Am Fam Physician. 2003 Mar 15;67(6):1392, 5-7. PMID 12674472.
21. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID 16686915.
22. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63(12):2215-24. PMID 15623677.
23. Gunner KB, Smith HD, Ferguson LE. Practice guideline for diagnosis and management of migraine headaches in children and adolescents: Part two. J Pediatr Health Care. 2008 Jan-Feb;22(1):52-9. PMID 18174091.
24. Geraud G, Lanteri-Minet M, Lucas C, et al. French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther. 2004 Aug;26(8):1305-18. PMID 15476911.
25. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. PMID 19708964.
26. Dowson AJ, Lipscombe S, Sender J, et al. New guidelines for the management of migraine in primary care. Curr Med Res Opin. 2002;18(7):414-39. PMID 12487508.
27. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. 2000 2000 Nov 15;62(10):2359-60. PMID 11126860.
28. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62. PMID 10993991.
29. Schuurmans A, van Weel C. Pharmacologic treatment of migraine. Comparison of guidelines. Can Fam Physician. 2005 Jun;51:838-43. PMID 15986940.
30. Whitlock EP, Lopez SA, Chang S, et al. AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):491-501. PMID 19540721.
31. Slutsky J, Atkins D, Chang S, et al. Comparing medical interventions: AHRQ and the Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. 2011/03/25 ed. Vol. March 2011. Rockville, MD: Agency for Healthcare Research and Quality; 2008:1-4. Available at www.effectivehealthcare.ahrq.gov.
32. Helfand M, Balshem H. Principles in Developing and Applying Guidance. 2008PMID 21433405.
33. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine. 2009 Aug 18;151(4):W65-94. PMID 19622512.
34. Norris S, Atkins D, Bruening W, et al. Chapter 4. Selecting observational studies for comparing medical interventions. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:56-68. Available at: www.effectivehealthcare.ahrq.gov.
35. Higgins J, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration; 2011.
36. Rothner AD. Complicated migraine and migraine variants. Curr Pain Headache Rep. 2002 Jun;6(3):233-9. PMID 12003695.
37. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160. PMID 14979299.
38. Hansen JM, Thomsen LL, Olesen J, et al. Calcitonin gene-related peptide does not cause the familial hemiplegic migraine phenotype. Neurology. 2008 Sep 9;71(11):841-7. PMID 18779512.
39. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2008 Sep 25;63(5):502-12. PMID 18823754.

40. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID 22008217.
41. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID 19595577.
42. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID 21784880.
43. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Sudbury, MA: Jones and Bartlett; 2003.
44. van der Velde G, van Tulder M, Cote P, et al. The sensitivity of review results to methods used to appraise and incorporate trial quality into data synthesis. Spine (Phila Pa 1976). 2007 Apr 1;32(7):796-806. PMID 17414916.
45. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006 Dec;59(12):1249-56. PMID 17098567.
46. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol. 2009;9:80. PMID 19961608.
47. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001.
48. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. Stat Med. 2007 Jan 15;26(1):37-52. PMID 16463355.
49. Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. Biom J. 2006 Apr;48(2):271-85. PMID 16708778.
50. Fu R, Gartlehner G, Grant M, et al. Chapter 9. Conducting quantitative synthesis when comparing medical interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:104-19. Available at: http://effectivehealthcare.ahrq.gov.
51. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. Eval Health Prof. 2001 Jun;24(2):152-64. PMID 11523384.
52. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998 Nov 7;317(7168):1309-12. PMID 9804726.
53. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. Acta neurologica Scandinavica; 1974. p. 109-15.
54. Sillanpää M. Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children. Headache; 1977. p. 28-31.
55. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. Cephalalgia. 1985 May;5 Suppl 2:145-8. PMID 2861907.
56. Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. Pediatrics. 1987 Apr;79(4):593-7. PMID 3822681.
57. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache. 1990 Apr;30(5):264-8. PMID 2191938.
58. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache; 1990. p. 264-8.
59. Battistella PA, Ruffilli R, Cernetti R, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache. 1993 Jan;33(1):36-9. PMID 8436497.
60. Winner P, Pearlman EM, Linder SL, et al. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Nov-Dec;45(10):1304-12. PMID 16324162.
61. Apostol G, Cady RK, Laforet GA, et al. Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache. 2008 Jul;48(7):1012-25. PMID 18705027.
62. Sheridan PH. Clinical Review. 2008:1-59. PMID NDA 21168: M02-488.
63. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics. 2009 Mar;123(3):924-34. PMID 19255022.
64. Wang F, Van Den Eeden SK, Ackerson LM, et al. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache. 2003 Jun;43(6):601-10. PMID 12786918.

65. Ashrafi MR, Shabanian R, Zamani GR, et al. Sodium Valproate versus Propranolol in paediatric migraine prophylaxis. Eur J Paediatr Neurol. 2005;9(5):333-8. PMID 16120482.
66. Bidabadi E, Mashouf M. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs. 2010 Aug 1;12(4):269-75. PMID 20593910.
67. Unalp A, Uran N, Ozturk A. Comparison of the effectiveness of topiramate and sodium valproate in pediatric migraine. J Child Neurol. 2008 Dec;23(12):1377-81. PMID 19073842.
68. Sartory G, Muller B, Metsch J, et al. A comparison of psychological and pharmacological treatment of pediatric migraine. Behav Res Ther. 1998 Dec;36(12):1155-70. PMID 9745800.
69. Lewis D, Paradiso E. A double-blind, dose comparison study of topiramate for prophylaxis of basilar-type migraine in children: a pilot study. Headache. 2007 Nov-Dec;47(10):1409-17. PMID 18052950.
70. Pandina GJ, Ness S, Polverejan E, et al. Cognitive effects of topiramate in migraine patients aged 12 through 17 years. Pediatr Neurol. 2010 Mar;42(3):187-95. PMID 20159428.
71. Winner P, Gendolla A, Stayer C, et al. Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. Headache. 2006 Nov-Dec;46(10):1503-10. PMID 17115983.
72. Trautmann E, Kroner-Herwig B. A randomized controlled trial of Internet-based self-help training for recurrent headache in childhood and adolescence. Behav Res Ther. 2010 Jan;48(1):28-37. PMID 19782343.
73. Sorge F, De Simone R, Marano E, et al. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. Cephalalgia. 1988 Mar;8(1):1-6. PMID 3282670.
74. Freitag FG. Topiramate prophylaxis in patients suffering from migraine with aura: results from a randomized, double-blind, placebo-controlled trial. Advanced Studies in Medicine; 2003. p. S562-s4.
75. Cruz MJ, Valencia I, Legido A, et al. Efficacy and tolerability of topiramate in pediatric migraine. Pediatric Neurology. 2009 Sep;41(3):167-70. PMID 19664530.
76. Apostol G, Lewis DW, Laforet GA, et al. Divalproex sodium extended-release for the prophylaxis of migraine headache in adolescents: results of a stand-alone, long-term open-label safety study. Headache. 2009 Jan;49(1):45-53. PMID 19040679.
77. Pakalnis A, Greenberg G, Drake ME, Jr., et al. Pediatric migraine prophylaxis with divalproex. Journal of Child Neurology. 2001 Oct;16(10):731-4. PMID 11669346.
78. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. Cochrane Database of Systematic Reviews. 2003(4):CD002761. PMID 14583952.
79. Jayapal S, Maheshwari N. Question 3. Topiramate for chronic migraine in children. Arch Dis Child. 2011 Mar;96(3):318-21. PMID 21317129.
80. Damen L, Bruijn J, Verhagen AP, et al. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. Cephalalgia. 2006 May;26(5):497-505. PMID 16674757.
81. Connock M, Frew E, Evans BW, et al. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. Health Technol Assess. 2006 Mar;10(7):iii, ix-118. PMID 16545206.
82. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007 Apr 18;297(15):1683-96. PMID 17440145.
83. Breslau N. Psychiatric comorbidity in migraine. Cephalalgia. 1998 Aug;18 Suppl 22:56-8; discussion 8-61. PMID 9793713.
84. Tfelt-Hansen P, Bjarnason NH, Dahl, et al. Evaluation and registration of adverse events in clinical drug trials in migraine. Cephalalgia. 2008 Jul;28(7):683-8. PMID 18498392.
85. Damen L, Bruijn J, Koes BW, et al. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. Cephalalgia. 2006 Apr;26(4):373-83. PMID 16556238.
86. Larsson B, Carlsson J, Fichtel A, et al. Relaxation treatment of adolescent headache sufferers: results from a school-based replication series. Headache. 2005 Jun;45(6):692-704. PMID 15953302.

87. Fichtel A, Larsson B. Relaxation treatment administered by school nurses to adolescents with recurrent headaches. Headache. 2004 Jun;44(6):545-54. PMID 15186298.
88. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005--a study from the Netherlands. Eur J Clin Pharmacol. 2008 Oct;64(10):1013-20. PMID 18618103.
89. Bazzano AT, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. Acad Pediatr. 2009 Mar-Apr;9(2):81-8. PMID 19329098.
90. Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. Drug Safety. 2002;25(1):1-5. PMID 11820908.
91. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol. 2002 Dec;54(6):665-70. PMID 12492616.
92. Ufer M, Kimland E, Bergman U. Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf. 2004 Mar;13(3):147-52. PMID 15072113.
93. Slutsky J, Atkins D, Chang S, et al. AHRQ series paper 1: comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):481-3. PMID 18834715.
94. Helfand M, Balshem H. AHRQ series paper 2: principles for developing guidance: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):484-90. PMID 19716268.
95. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35. PMID 11306229.

Introduction

In the United States, migraine affects a significant number of children: 5 percent of boys[5, 6] and 7.7 percent of girls.[7, 8] Childhood migraine is more prevalent in lower income families.[7] Among adolescents, migraine is more prevalent in whites than African Americans.[7]

According to the International Classification of Headache Disorders (ICHDII), migraine is a common disabling primary headache disorder manifesting in attacks that last from 4 to 72 hours.[1,2] Migraine headaches range from moderate to very severe[3] and are sometimes debilitating.[4] Childhood migraine is more prevalent in lower income families.[7] Among adolescents, migraine is more prevalent in whites than African Americans.[7]

Migraine frequency is divided into episodic and chronic.[2] Episodic migraine is characterized by ≤15 and chronic migraine by ≥15 headache days per month. Chronic migraine affects 2 percent of children and adolescents.[9] Migraine significantly affects children's physical, psychological, and social well-being and can impose serious lifestyle restrictions.[9] Indeed, the majority of adolescents with chronic migraine have migraine-related disability.[9] Yet, according to the Chronic Daily Headache in Adolescents Study (C-dAS), fewer than half of adolescents with chronic migraine had visited a healthcare provider, and fewer than one in five had taken medications to prevent headaches during the previous month.[9]

Migraine pain results primarily from increased activity of several agents that regulate blood vessels and sensory function of the brain.[1] In about 15 percent of patients, including children, migraine attacks may be accompanied by aura (visual, sensory, or language symptoms). Other accompanying symptoms may include photophobia (excessive sensitivity to light), phonophobia (fear of loud sounds), osmophobia (hypersensitivity to smells), nausea, or vomiting.[3]

Prospective epidemiologic studies that followed children with migraine for decades demonstrated that around 20 percent became migraine-free before the age of 25; boys significantly more often than girls.[95, 96] However, for more than half of children with migraine, the attacks continued to middle and older age.[95]

Childhood migraine, whether chronic or episodic, can have a serious detrimental impact on daily life. Approximately 31 percent of children with migraine missed at least 1 day of school in the previous 3 months because of the condition,[10] which overall has been shown to impair learning and school productivity by ≥50 percent.[10] Many children with frequent or severe attacks need treatment, which falls into two categories: (1) treatment for acute attacks and (2) migraine prevention. Symptomatic treatment for acute migraine in children includes nonsteroid anti-inflammatory agents, triptans, or antiepileptics.[97] Our review focuses on preventive treatments for childhood migraine.

Preventive medications are presumed to address the pathophysiology of migraine.[11, 12] The four drugs approved by the U.S. Food and Drug Administration (FDA) for migraine prevention in adults come from different drug classes and include propranolol, timolol, topiramate, and divalproex sodium.[13] The FDA has approved no drugs for migraine prevention in children; therefore, pediatricians prescribe either drugs approved for adults, or off-label drugs (approved for clinical conditions other than migraine prevention).[13, 14] These drug classes cause common and serious adverse effects, including metabolic and hormonal abnormalities.[15-19] Therefore, migraine preventive drug choices are based on efficacy and safety of approved and off-label drugs.[20-27]

Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month,[1] while others suggest it for those who experience a headache on most days of the month.[22, 98, 99] Researchers have yet to fully examine long-term migraine

frequency and adverse effects with preventive treatments.[3] Preventive treatment aims to eliminate headache pain.[20, 21, 28] Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency by ≥50 percent after 3 months.[3] In addition to pain relief, preventive drugs can also decrease severity of migraine attacks and reduce restrictions in daily activities and schooling.[29, 30]

Gaps remain in the published literature on preventive treatments for migraines in children. Published systematic reviews have focused on efficacy of specific drugs rather than comparative effectiveness of all available pharmacological and nonpharmacological treatments, including multidisciplinary migraine management programs. Furthermore, syntheses of evidence have neither consistently assessed risk of bias in individual studies nor evaluated strength of evidence about benefits and harms with available treatments.

Our review focuses on the comparative effectiveness and safety of drugs for preventing migraine attacks in children in ambulatory care settings; our results will help inform related treatment recommendations.

After discussion with key informants and the Technical Experts Panel,[31] we formulated a list of eligible pharmacological classes. We specifically opted not to synthesize studies of flunarizine, because it lacks FDA approval. We conducted a comprehensive literature review following the principles in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program[32, 33] and PRISMA guidelines (registration number is CRD42011001858)[34]

Key Questions

Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children?

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in children?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) improve safety of the treatments?

Question 3. Which characteristics of children predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks?

Methods

Search Strategy

We searched for published studies in several databases, including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database. We searched the FDA Web site to find medical and statistical reviews of the eligible drugs. We searched clinical trial registries including ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry to find ongoing, completed, and published trials of migraine prevention. We requested Scientific Information Packets from appropriate manufacturers (shown in Appendix A) per usual procedures. We searched for the studies published in English up to March 29, 2012. We did not contact the investigators of the primary studies for missing data or clarifications.

The EPC developed a search strategy based on relevant medical subject heading (MeSH®) terms, text words, and weighted word-frequency algorithms to identify related articles. Exact search strategies can be found in Appendix A. Ongoing completed studies are shown in Appendix B.

Searches for relevant literature involved several steps: (1) evaluating previously published systematic reviews,[100] (2) conducting a comprehensive literature search in the above databases to retrieve identified references, (3) screening abstracts against the inclusion/exclusion criteria, and (4) reviewing full-text articles of eligible studies to determine potential inclusion in the synthesis.

Eligibility

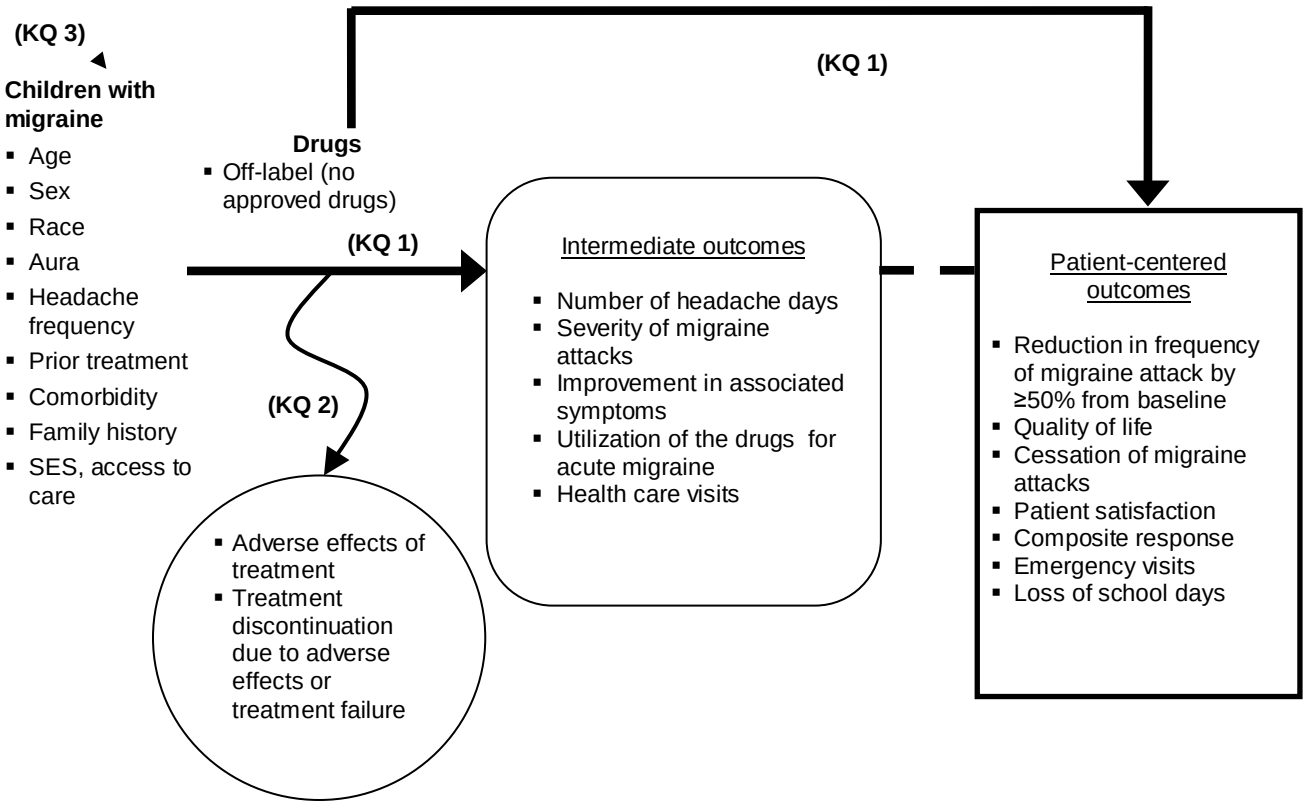
We followed the AHRQ *Methods Guide* to select evidence from controlled trials and observational studies.[35] Three investigators independently determined study eligibility according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.[36] To assess treatment benefits, we included randomized controlled trials (RCTs). To assess treatment harms, we included all available evidence from RCTs and observational studies.[35 37] We defined harms as a totality of all possible adverse consequences of an intervention.[37] We analyzed harms regardless of how authors perceived causality of treatments.

We defined the target population, eligible preventive treatments, outcomes, time, and setting following the PICOTS framework (Population, Intervention, Comparator, Outcome, Timing, and Setting) (Appendix C Analytical framework). We formulated a list of eligible interventions after discussions with key informants and technical experts, and after consideration of public comments.

Inclusion Criteria

1. Original epidemiologic studies that aimed to examine preventive pharmacological treatments for migraine.
2. Publication in English.
3. Target population of community-dwelling children with episodic migraine, chronic daily headache, or chronic migraine defined according to International Headache Society criteria for chronic migraine.[22]
4. Eligible intermediate and patient-centered outcomes as listed in the analytical framework (Figure 1).
5. Drugs examined in clinical trials.

Figure 1. Analytical framework (developed by following the AHRQ *Methods Guide* and the methods of the U.S. Preventive Services Task Force)[101-103]



Abbreviations: KQ = key question; SES = socioeconomic status

We reviewed original clinical studies that included children with migraine, comorbid headache disorders, or tension headache as long as they examined prevention of migraine. Episodic or chronic migraine as defined by the Headache Classification Committee of the International Headache Society[22] does not include migraine variants or migraine equivalents with atypical symptomatic pain in regions other than the head.[2, 38] Therefore, we exclude these studies.

Exclusion Criteria

1. Studies of treatments aimed at acute migraine attacks.
2. Studies that involved patients with migraine variants, such as basilar migraine, childhood periodic syndromes, retinal migraine, complicated migraines, and ophthalmoplegic migraine; hospitalized patients; or patients in emergency rooms.[2, 38, 39] Studies of short-term prevention of migraine, including menstrual migraines. We also excluded hemiplegic migraine, a pathophysiologically distinct disorder with its own classification.[39]
3. Studies that included some pediatric patients with migraine but did not separately report those outcomes.
4. Studies that involved surgical treatments for migraine.

5. Preclinical pharmacokinetic studies of eligible drugs; studies that examined the pathophysiology of migraine reporting instrumental measurements or biochemical outcomes.
6. Studies that did not test the associative hypotheses and did not provide adequate information on tested hypotheses (e.g., least square means, relative risk).
7. Studies that examined eligible drugs on populations with other diseases.
8. Studies evaluating the efficacy of nonpharmacological treatments or economic outcomes that are beyond the scope of this review.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies according to recommendations from the *Cochrane Handbook for Systematic Reviews of Interventions*.[36] First, we classified the study design as interventional (an RCT, a nonrandomized controlled clinical trial, or a nonrandomized uncontrolled clinical trial) or observational (cohort or case-control studies, cross-sectional studies, or case series).

Then, using the criteria from the Cochrane tool for bias in interventional studies,[40] we evaluated:

Random allocation of the subjects to the treatment groups.

Masking of the treatment status.

Adequacy of allocation concealment.

Adequacy of randomization according to baseline similarity of the subjects in treatment groups by demographics, migraine frequency and severity, and response to previous treatments.

Intention-to-treat principles.

Selective outcome reporting when compared to the posted protocols (when trials were registered) or methods section in the articles.

We assumed a low risk of bias when RCTs met all the risk of bias criteria; a moderate risk of bias if at least one of the risk of bias criteria was not met; and a high risk of bias if two or more risk of bias criteria were not met. We concluded an unknown risk of bias for the studies with poorly reported risk of bias criteria. Masking of treatment status was not feasible for RCTs that examined nondrug therapies as comparators. We evaluated risk of bias in such RCTs using four other criteria described above. We appraised risk of bias in nonrandomized studies according to selection, attrition, and detection biases.[41]

Since all outcomes in the review are self-reported, masking of outcome assessment was not essential in evaluating risk of bias, but masking of treatment was. We evaluated disclosure of conflict of interest by the authors of individual studies and funding sources but did not use this information to downgrade quality of individual studies.

Grading the Evidence for Each Key Question

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome, and treatment discontinuation due to harms.[42] As part of our strength of evidence assessment we also looked at dose-response association, strength of association, and reporting bias. We evaluated the strength of the association, defining *a priori* a large effect when relative risk is >2 or <0.5 and a very large effect when relative risk is >5 or <0.2.[36] We defined low magnitude of effect when the relative risk was significant but <2.We

defined reporting bias as publication bias, selective outcomes reporting, and multiple publication bias. We did not perform formal statistical tests quantifying the biases.[44]

We defined high level of evidence on the basis of consistent findings from well-designed RCTs (Table 1). We downgraded strength of evidence to moderate if at least one of the four strength of evidence criteria (risk of bias, directness, consistency, and precision) was not met; for example, the studies had moderate risk of bias or the results were not consistent or precise. We downgraded strength of evidence to low if two or more criteria were not met. We defined evidence as insufficient when a single study with high risk of bias examined treatment effects or associations.

Table 1. Criteria to rank strength of evidence

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

Assessing Applicability

We estimated applicability of the sample by evaluating the selection of children with migraine in observational studies and clinical trials.[45] Studies of community-dwelling children with 6 months or more followup with drug treatments had high applicability, as did large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases.

Data Extraction

Researchers used standardized forms to extract data (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041370_1-t_yAjBY2Cn). We conducted a double independent quality control for the data extracted from RCTs; one reviewer abstracted an article and a second reviewer checked the abstracted data for accuracy. We assessed errors by comparing established ranges for each variable with data charts from the original articles. Any detected discrepancies were discussed. We abstracted the information relevant to the PICOTS framework. We abstracted minimum datasets to reproduce the results presented by the authors. For categorical variables, we abstracted the number of events among treatment groups to calculate rates, relative risk, and absolute risk differences. Means and standard deviations of continuous variables were abstracted to calculate mean differences with a 95 percent confidence interval (CI).

For RCTs in the quantitative analysis set, we abstracted the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles. We abstracted the time when the outcomes were assessed as weeks from randomization and the time of followup after treatments.

We abstracted inclusion and exclusion criteria, drug regime and doses, and patient characteristics including demographics, migraine definition, baseline frequency, severity, and prior treatment status as factors that could modify treatment effects. We abstracted sponsorship of the studies and conflict of interest by the authors.

Data Synthesis

We summarized the results into evidence tables. We focused on patient-centered outcomes, such as reduction in migraine attacks by ≥50 percent from baseline, quality of life, patient satisfaction, and composite outcomes that included migraine frequency and severity. We incorporated risk of bias in individual studies into the synthesis of evidence by using individual risk of bias criteria rather than a global score or a ranking category of overall risk of bias.[46, 47] Synthesis of evidence about comparative benefits and safety with drugs from individual RCTs was restricted to studies with low risk of bias.[20]

We synthesized the evidence according to population characteristics that could modify treatment effects, including age, sex, and race; duration of migraine; baseline frequency and severity of acute migraine attacks; presence of aura; previous drug treatments; history of drug overuse; and other patient characteristics described in the PICOTS framework. We addressed the role of comorbidities and concomitant treatments in association with patient-centered outcomes. When possible, based on the reporting in original studies, we conducted subgroup and sensitivity analyses according to patient characteristics, drug dose, and timing of followup.

Using Meta-Analyst[48] and STATA®[49] software at a 95 percent CI, we calculated the relative risk and absolute risk difference from the abstracted events and the mean differences in continuous variables from the reported means and standard deviations. We used a logarithmic scale to analyze the adjusted regression coefficient with a standard error of association between treatments and patient-centered outcomes. We used correction coefficients and intention to treat as recommended calculations for missing data.[36] We synthesized sparse data defined as rates less than 2 percent, and calculated fixed Mantel-Haenszel relative risk and Peto odds ratio.[52] When studies had no events with active, control, or both treatments, we used correction coefficients and calculated double arcsine transformation for comparing two proportions and odds ratios from random-effects generalized nonlinear mixed-effect models.[48, 104-107]

Pooling criteria for Key Questions 1 and 2 included the same active drug treatments and comparators and the same definitions of the outcomes. We calculated standardized mean differences for different continuous measures of the same outcome.

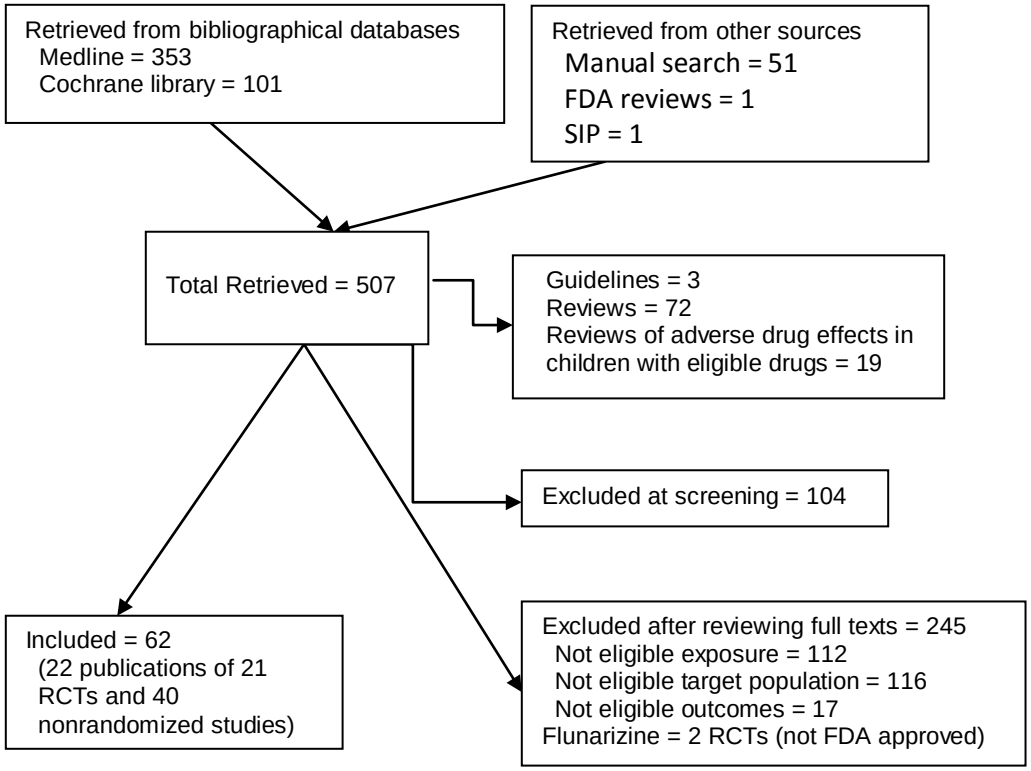
We tested consistency in the results by comparing the direction and strength of the association[42] and assessed heterogeneity in results with Chi-square and I-square tests.[50, 51] We explored heterogeneity with meta-regression and sensitivity analysis, reporting the results from random effects models only.[108] Using the random effects model we incorporated into the pooled analysis any differences between trials in patient populations, baseline rates of the outcomes, dosage of drugs, and other factors.[52] We explored heterogeneity by risk of bias criteria, disclosed conflicts of interest, study sponsorship, dose and duration of drug treatments, time of followup, inclusion of minorities, proportion of women and elderly adults, and other patient characteristics described above. To avoid ecological fallacy, we did not use patient level variables (for example, mean age or body mass index) in meta-regression.[108] We focused on direct comparisons and synthesized evidence from head-to-head comparative effectiveness studies.

The number needed to treat to achieve one event of a patient-centered outcome was calculated as the reciprocal of statistically significant absolute risk differences (ARD) in rates of outcome events in the active and control groups.[49, 53] We calculated means and 95 percent CIs for the number needed to treat as reciprocal of pooled ARD when ARD is significant.[54] The number of avoided or excess events (respectively) per population of 1,000 is the difference between the two events rates multiplied by 1,000. We calculated Bayesian odds ratios[48, 107] with 95 percent credible intervals. All calculations were performed at a 95 percent confidence level.

Results

We retrieved 507 references, excluded 353 references, and included 22 references for 20 RCTs and 40 publications of nonrandomized studies (Figure 2). We found one FDA review that evaluated a clinical trial of divalproex sodium in the prophylactic treatment of migraine headache in adolescents.[64] Of 16 completed clinical trials registered in ClinicalTrials.gov, three were published. Appendix D provides evidence tables with the results from the included studies. Appendix E presents all excluded studies with exact reasons for exclusion.

Figure 2 Study Flow



Study Overview

Characteristics

The applicability of the enrolled subjects to the target population was good**.** Most trials were conducted in Western countries and recruited children and adolescents in clinics. Only two trials recruited participants from the community. We analyzed baseline characteristics of included children and concluded that enrolled patients represent epidemiology of migraine in the target population (Appendix Table D1). Caucasian girls constituted more than half of all enrolled subjects. Many enrolled subjects were overweight according to the mean age, with the average body mass index being 23±1.6. Children had migraine for an average 3.5 years, and suffered from eight migraine attacks per month. Most trials defined migraine according to diagnostic criteria of the International Headache Society (Appendix Table D2). Reporting other characteristics of children was poor. More than half the trials failed to report family history of

migraine, children's socioeconomic status, baseline comorbidity, prior treatments, overuse drugs for acute migraine, or adherence to assigned treatments.

Based on infrequently reported trial flows, we estimated that investigators had to screen two to four children to enroll one (Appendix Table D3). The trials lasted in average 20 weeks (ranging 6 to 52 weeks). Attrition rates averaged around 9 percent.

Risk of Bias

We concluded low risk of bias in 50 percent, moderate risk of bias in 25 percent, and unclear risk of bias in 25 percent of all included trials (Appendix Table D4). Most trials were double blind; however, randomization was adequate in just nine trials. Trials lasted an average of 21 weeks after a run-in period of 5 weeks (Appendix Table D1). We concluded high risk of bias in nonrandomized studies that did not address selection bias in study design and analyses.

Risk of bias was associated with journals of the publication. Some journals published RCTs with poorly reported trial design and conduct (Appendix Table D5). Most RCTs were published in the journal *Headache*; only 60 percent of all published RCTs had low risk of bias.

Risk of bias was associated with funding of the trials (Appendix Table D5). Industry-funded RCTs had lower risk of bias than trials funded by grants, combined, or other sources. Most well-designed RCTs failed to report sponsorship of studies.

Trials aimed to examine prevention of episodic migraine and adverse effects but rarely reported statistical power to detect statistically significant differences in outcomes.

Question 1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children?

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?

Ten randomized placebo-controlled RCTs examined efficacy of drugs for migraine prevention in children (Appendix Table D6).[55-65] The trials included 1,125 children ages 9 to14. Sample size of RCTs averaged 112.5±109 children, with boys constituting 51 percent. Half of the RCTs did not report ethical approval by institutional review boards or consent of the participants (Appendix Table D7). RCTs had low risk of bias, with double-blind design and low risk of bias in eight of 10 trials (Appendix Table D8). Eligible trials defined clinically important migraine prevention as a complete cessation of migraine attacks and a reduction in monthly migraine frequency by ≥50 or 75 percent.

Off Label Pharmacological Agents

Table 2 summarizes the effectiveness of off label pharmacological agents.

Antiepileptic Drugs

Topiramate

Topiramate, 100 to 200 mg/day, was no more effective than placebo in reducing monthly migraine attacks by ≥50 percent (two RCTs of 298 children, moderate strength of evidence)

(Appendix Tables D9-10).[62, 65] Topiramate increased the likelihood of ≥75 percent reduction in migraine days more often than placebo in a single double-blind RCT (Appendix Table D11).[62]

Using this statistically significant risk difference, we estimated that 181 children (95 percent CI, 52 to 311) per 1,000 treated experienced ≥75 percent reduction in migraine days due to topiramate, 200 mg/day.[62] Absolute reduction in migraine days with topiramate, 50 to 200 mg/day, was not better than with placebo in pooled analysis of two double-blind RCTs (Appendix Table D12).

Divalproex

Divalproex sodium, 250 to 1000 mg/day, was no more effective than placebo in reducing monthly migraine by ≥50 percent in one low risk of bias RCT (305 children, low strength of evidence) (Appendix Table D13).[63]

The efficacy of divalproex sodium was examined in two low risk of bias RCTs of 610 children.[63, 109] Divalproex sodium in doses of 250, 500, or 1,000 mg/day was not better than placebo in preventing migraine attacks, decreasing migraine days, or decreasing acute drug use (Appendix Tables D14-D16).[63, 64]

Antidepressants

Trazodone was more effective than placebo in reducing frequency and duration of migraine attacks by 1.6 per month, and at reducing duration of migraine attacks by 8.2 hours per attack (one RCT of 40 children, low strength of evidence).[61] A single small double-blind crossover RCT examined the efficacy of trazodone versus placebo (Appendix Table D17).[61] Trazodone in a dose 1mg/kg/day significantly decreased frequency of migraine attacks by 1.6 per month and duration of migraine attacks by 8.2 hours per attack (Appendix Table D17).[61]

Beta blockers

Propranolol resulted in a complete cessation of migraine attacks more often than placebo (one RCT of 28 children, low strength of evidence) (Appendix Table D18).[55]

Two small RCTs examined the efficacy of propranolol. One small double-blind low risk of bias RCT demonstrated that children experienced a complete cessation of migraine attacks more often with propranolol than with placebo (Appendix Table D19).[55] We estimated that 713 children per 1,000 treated would have no migraine attacks with propranolol.[55] In a second small crossover RCT, propranolol failed to show a significant reduction in migraine days compared with placebo (Appendix Table D20).[58]

Calcium Channel Antagonists

Nimodipine was better than placebo in decreasing migraine days (one RCT of 37 children, low strength of evidence).

Nimodipine was better than placebo in decreasing migraine days (mean difference 0.9, 95 percent CI, 0.5 to 1.3) (Appendix Table D21), but not duration of migraine attacks.[59]

Antiadrenergic Drugs

Clonidine was no more effective than placebo in preventing migraine, reducing migraine duration or severity, or reducing use of drugs for acute treatment (one RCT of 57 children, low strength of evidence) (Appendix Table D22). The efficacy of antiadrenergic drug clonidine was examined in one small double-blind low risk of bias RCT.[56] Clonidine performed no better than

placebo in achieving complete cessation of migraine or in decreasing migraine days, severity, or need for acute drug therapy for single attacks (Appendix Table D23).[56]

Magnesium Oxide

A single RCT demonstrated no significant differences with magnesium oxide and placebo in migraine frequency.[66] Magnesium oxide reduced severity of migraine attacks relative to the placebo group.[66]

b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?

Limited evidence from individual RCTs suggested no differences in migraine prevention with examined drugs including propranolol, valproate, and topiramate.

Three RCTs examined comparative effectiveness of drugs for migraine prevention in children (Appendix Tables D24 and D25).[67-69] The trials included 231 children, averaging 9 to 11 years old. The sample size of RCTs averaged 77±38 children; boys constituted 60 percent of subjects. The trials had moderate[68] or unclear risk of bias (Appendix Table D26).

Two RCTs of 183 children examined comparative effectiveness of sodium valproate versus propranolol, and found no significant differences between the drugs for achieving complete cessation of headache attacks or reduction by ≥50 percent from baseline in frequency of migraine attack (low strength of evidence). (Appendix Table D27).[67, 68] Sodium valproate, 15 to 30 mg/kg/day, was more effective than propranolol, 2 to 3 mg/kg/day, in reducing baseline headache frequency by >70 percent in a single RCT (Appendix Table D28).[68] The drugs did not differ in effects on reduction in migraine severity or response to acute drugs for migraine attacks.

One RCT of 48 children examined comparative effectiveness of topiramate versus sodium valproate (low strength of evidence). The two drugs did not differ in their effects on migraine frequency, intensity, duration, or Pediatric Migraine Disability Assessment Score (Appendix Table D29).[69]

c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?

Limited evidence from individual RCTs suggested better effectiveness of nonpharmacological treatments than beta blockers for preventing migraine in children. Two small RCTs compared drugs with active nonpharmacological treatments (Appendix Tables D30 and D31).[58, 70] We concluded unclear risk of bias in both trials because the authors provided insufficient details about methodology (Appendix Table D32).

One RCT of 43 children examined comparative effectiveness of metoprolol versus nonpharmacological treatments, including stress management combined with either progressive relaxation training or cephalic vasomotor feedback, and found no significant differences in the percentage of children who improved by ≥50 percent in the headache index (low strength of evidence) (Appendix Table D33).[70] In fact, metoprolol tended to be less effective in preventing migraine or reducing migraine severity than stress management combined with either progressive relaxation training or cephalic vasomotor feedback (Appendix Table D34).[70] The differences, however, did not achieve statistical significance.

Comparative effectiveness of propranolol versus nonpharmacological treatments was examined in one RCT of 33 children (low strength of evidence) (Appendix Table D35).[58] The trial found more frequent migraine with the drug than with self-hypnosis (mean difference of nine monthly migraine attacks, 95 percent CI, 4 to 14) (Appendix Table D35).[58]

d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?

No studies compared combined pharmacological and nondrug preventive treatments with mono-drug therapy in children.

e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Four RCTs published in five articles[63-65, 71, 72] and one pooled analysis of three RCTs[73] examined the dose-response effects of preventive antiepileptic drugs in children (Appendix Tables D36 and D37). All RCTs were double blind with low risk of bias (Appendix Table D38).

Topiramate

A higher dose of topiramate compared to a lower dose (100 versus 25 mg) demonstrated no consistent significant difference in migraine prevention (Appendix Table D39).[65, 71]

Two small RCTs examined a higher and lower dose of topiramate (100 versus 25 mg) for reducing migraine frequency by 50 percent in children. The smaller RCT found no differences in a response rate,[71] while the larger RCT found that more children experienced ≥50 percent reduction in migraine attack with the larger dose of the drug.[65]

Higher doses of topiramate (100 to 200 mg/day) resulted in no greater reduction in disability score or migraine duration (Appendix Table D40).[65, 71]

Divalproex Sodium

Higher doses of divalproex sodium (500 to 1,000 versus 250 mg/day) resulted in no significantly better migraine prevention in a single RCT that examined this association (Appendix Table D41). Higher doses of divalproex sodium resulted in no greater reduction in migraine days or acute drug use (Appendix Table D42).[63, 64]

e2. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

Multidisciplinary drug management including cognitive-behavioral training was more effective than usual care combined with an educational intervention in preventing migraine in children and adolescents (one RCT of 68 children, low strength of evidence).[74]

A single RCT of 68 children and adolescents 10 to 18 years old examined internet-based multimodal drug management including cognitive-behavioral training (CBT) or applied relaxation compared to usual care (Appendix Table D43).[74]

A multimodal CBT focused on stress management (perception of own stress symptoms, coping with stress), progressive relaxation techniques, cognitive restructuring (identification of dysfunctional cognitions regarding headache and self-assurance strategies such as being

proactive and sensitive to one's own needs), and problem solving. The participants communicated through email with a multidisciplinary team of trial coordinators.[74] The applied relaxation included progressive relaxation, cue-controlled (triggered by key word or an image) relaxation, and differential relaxation.[74] Multimodal CBT was more effective than education in reducing migraine frequency by ≥50 percent (relative risk 4.0, 95 percent CI 1.0 to 16.0) (Appendix Table D44).[74] We estimated that 310 children per 1,000 treated with multimodal CBT would experience ≥50 percent reduction in migraine frequency (95 percent CI, 70 to 550). The effect, however, did not last at 6 months of followup.[74] Migraine frequency (Appendix Table D45) and quality of life did not differ with internet-based self-management versus an education program (Appendix Table D46).[74]

Question 2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults and children?

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?

Topiramate and divalproex sodium resulted in treatment discontinuation due to adverse effects (Table 3). Topiramate significantly increased risk of anorexia, weight loss, paresthesia, and upper respiratory tract infection.

Ten randomized trials[56, 57, 61-66, 72, 75, 76] and one pooled analysis of three RCTs[73] examined the safety of drugs for migraine prevention in children (Appendix Table D47). The trials included 1,418 children. Sample size averaged 118±94 children, with boys constituting 45 percent of participants. All RCTs were double blind. Based on all risk of bias criteria, we concluded that all RCTs had low risk of bias except three with moderate risk of bias.[62, 66, 76] Forty nonrandomized studies reported harms with migraine preventive drugs in children (Appendix Table D48).

Adverse Effects of Antiepileptic Drugs

Topiramate

Treatment discontinuation due to adverse effects was greater with topiramate than placebo in a pooled analysis of four RCTs (low strength of evidence) (Appendix Tables D49 and D50).[62, 65, 72, 73] We estimated that 55 children per 1,000 treated with topiramate would discontinue treatment because of adverse effects (Table 4).[65, 72]

Nonrandomized studies suggested that 19 percent of children discontinued topiramate treatments due to bothersome adverse effects.[77]

A single RCT reported that 260 children per 1,000 treated with topiramate (95 percent CI, 30 to 480) would experience adverse effects (Appendix Table D51).[65] Our pooled analysis of individual adverse effects (Appendix Table D52) demonstrated a significant increase in risk of anorexia, weight loss, paresthesia, and upper respiratory tract infection with topiramate. We estimated that 87 children per 1,000 treated with topiramate would experience unintended weight loss (95 percent CI, 24 to 150) and upper respiratory tract infection would be diagnosed in 105 children per 1,000 (95 percent CI, 29 to 182) (Table 5).[62, 65, 73]

A single case report described development of the "Alice in Wonderland syndrome,"[110] in which the treated girl described a distortion of the body image and perception of disproportional body, arms, and head size, with a dose of 75 mg/day, but not on lower doses of topiramate (Appendix Table D48).[110]

Divalproex Sodium

Treatment discontinuation due to adverse effects with divalproex sodium compared to placebo was greater with 1,000 mg/day but not with 250 mg/day in pooled analysis of two RCTs (low level of evidence) (Table 4).[63, 64]

Treatment discontinuation due to treatment failure did not differ between divalproex sodium and placebo (Appendix Table D53).[63] Pooled analyses of two RCTs demonstrated that 140 children per 1,000 treated with divalproex sodium would experience adverse effects (95 percent CI, 30 to 250) (Appendix Table D54).[63, 64]

Nonrandomized studies suggested that 84 percent of children would experience adverse effects with divalproex,[78] and 17 percent discontinued treatment due to bothersome adverse effects.[79]

A single RCT examined risk of individual adverse effects and found no significant differences with active drug versus placebo (Appendix Table D55).[63] This double-blind trial had low risk of bias, but not enough power to detect significant differences in rare adverse events with the drug versus placebo (sparse data).[63]

Antidepressants

A single low risk of bias RCT found that treatment discontinuation did not differ between the antidepressant trazodone and placebo in 40 children with migraine (Appendix Table D56).[61] One retrospective chart review demonstrated that of 14 patients taking amitriptyline, 36 percent discontinued it due to side effects at 16 weeks. [111]

Beta Blockers

A single RCT demonstrated that risk of adverse effects did not differ between propranolol and placebo (Appendix Table D57).[76]

Antiadrenergic Drugs

A single RCT demonstrated that risk of treatment discontinuation due to adverse effects did not differ between the antiadrenergic drug clonidine and placebo (Table 4).[56] This double-blind RCT demonstrated that clonidine significantly increased risk of fatigue (Appendix Table D 58).[56] We estimated that 220 children of 1,000 treated would become fatigued (95 percent CI, 30 to 410) with clonidine.[56] Other adverse effects, including drowsiness or difficulty in reading, did not differ between clonidine and placebo.[112]

Magnesium Oxide

A single RCT demonstrated no difference between magnesium oxide and placebo for risk of treatment discontinuation, or for treatment discontinuation due to treatment failure or adverse effects (Appendix Table D59).[66]

Botulinum Toxin

One small nonrandomized study demonstrated that 8 percent of adolescents treated with botox 100U every 3 months experienced blurred vision and ptosis, and burning sensations at all injection sites[113] (Appendix Table D48).

b. What are the harms from preventive pharmacologic treatments when compared to active pharmacological treatments?

Comparative Safety of Topiramate Versus Sodium Valproate

A single RCT found no differences in adverse effects with topiramate and sodium valproate for 12 weeks in 40 children with migraine (Appendix Table D60).[69]

c. How might approaches to drug management (such as patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?

We found no studies that examined how drug management can improve safety of migraine preventive medications in children.

Question 3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in children and adults?

We found no studies that examined how specific characteristics of children can predict effectiveness or safety of migraine preventive medications. No studies examined which characteristics of children might modify effectiveness or safety with preventive drugs.

Table 2. Migraine prevention in children

Outcome	Active	Control	RCTs Reference	Children	Rate active, %	Rate control, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Complete cessation of headache attacks	**Propranolol**	**Placebo**	**1[55]**	**28**	**84.6**	**13.0**	**6.3 (1.7 to 23.5)**	**0.71 (0.45 to 0.97)**	**1 (1 to 2)**	**713 (452 to 974)**	**Low**
	Clonidine	Placebo	1[56]	57	10.7	24.1	0.4 (0.1 to 1.5)	-0.13 (-0.33 to 0.06)			Low
	Sodium valproate	Propranolol	2[67,68]	183	17.1	15.4	1.2 (0.6 to 2.2)	0.02 (-0.09 to 0.12)			Low
Reduction by 50% in migraine attack frequency	Topiramate	Placebo	2[62,65]	298	58.2	45.7	1.3 (0.9 to 1.8)	0.15 (-0.06 to 0.37)			Moderate
	Divalproex sodium	Placebo	1[63]	305	49.0	45.0	1.1 (0.8 to 1.5)	0.04 (-0.12 to 0.20)			Low
	Propranolol	Placebo	1[55]	28	7.7	0.0	3.4 (0.2 to 77.6)	0.08 (-0.11 to 0.26)			Low
	Clonidine	Placebo	1[56]	57	32.1	27.6	1.2 (0.5 to 2.6)	0.05 (-0.19 to 0.28)			Low
	Sodium valproate	Propranolol	2[67]	183	69.5	74.3	0.9 (0.7 to 1.2)	-0.07 (-0.30 to 0.15)			Low
	Metoprolol	**Progressive relaxation training + stress management**	**1[70]**	**28**	**38.5**	**80.0**	**0.5 (0.2 to 1.0)**	**-0.42 (-0.75 to -0.08)**	**-2 (-12 to -1)**	**-415 (-748 to -82)**	**Low**
	Metoprolol	Cephalic vasomotor feedback + stress management	1[70]	28	38.5	53.3	0.7 (0.3 to 1.7)	-0.15 (-0.51 to 0.22)			Low
	Applied relaxation	Educational intervention	1[74]	41	40.9	26.3	1.6 (0.6 to 3.8)	0.15 (-0.14 to 0.43)			Low
	Multimodal cognitive-behavioral training (CBT)	Educational intervention	1[74]	43	29.2	26.3	1.1 (0.4 to 2.9)	0.03 (-0.24 to 0.30)			Low
	Multimodal cognitive-behavioral training (CBT)	Applied relaxation	1[74]	46	29.2	40.9	0.7 (0.3 to 1.6)	-0.12 (-0.39 to 0.16)			Low

Table 2. Migraine prevention in children (continued)

Outcome	Active	Control	RCTs Reference	Children	Rate active, %	Rate control, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Reduction for need for temporary drug therapy for single attacks	Clonidine	Placebo	1[56]	57	50.0	34.5	1.5 (0.8 to 2.7)	0.16 (-0.10 to 0.41)			Low
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1[69]	48	NA	NA	-0.9 (-5.6 to 3.8)	0.00 (0.00 to 0.00)			Low

Bold - significant differences at 95% confidence level

Table 3. Evidence of treatment discontinuation due to adverse effects with migraine preventive drugs versus placebo in children

Drug	RCTs Reference	Children	Conclusion	Strength of Evidence
Divalproex sodium, 1000 mg	2[64 63]	296	Divalproex sodium 1000 mg resulted in greater treatment discontinuation rates vs. placebo	Low
Divalproex sodium, 250 mg	2[64 63]	312	Divalproex sodium 250 mg did not result in greater treatment discontinuation rates vs. placebo	Low
Divalproex sodium, all doses	2[64 63]	755	Divalproex sodium resulted in greater treatment discontinuation rates vs. placebo	Low
Topiramate, 100 mg	2[65, 72]	136	Topiramate 100 mg did not result in greater treatment discontinuation rates vs. placebo	Low
Topiramate, 50-100 mg	2[65, 72]	272	Topiramate 50-100 mg, resulted in greater treatment discontinuation rates vs. placebo	Low
Clonidine	1[56]	57	Clonidine 25-50 µg did not result in greater rates of treatment discontinuation vs. placebo; the data is sparse	Insufficient

Table 4. Treatment discontinuation due to adverse effects with migraine preventive drugs versus placebo in children

Drug	RCTs Reference	Children	Rate with drug, %	Rate with placebo, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat (95% CI)	Attributable events per 1000 treated (95% CI)	Strength of evidence
Divalproex sodium, 1000 mg	**2[63,64]**	**296**	**9.3**	**1.4**	**6.8 (1.6 to 29.5)**	**0.08 (0.03 to 0.13)**	**13 (8 to 34)**	**80 (29 to 130)**	**Low**
Divalproex sodium, 250 mg	2[63,64]	312	2.4	1.4	1.8 (0.3 to 9.5)	0.01 (-0.02 to 0.04)			Low
Divalproex sodium, all doses	2[63,64]	755	4.6	1.4	2.9 (1.0 to 8.3)	0.02 (-0.01 to 0.06)			Low
Topiramate, 100mg	2[65,72]	136	8.6	3	2.8 (0.6 to 13.5)	0.06 (-0.02 to 0.13)			Low
Topiramate, 50-100 mg	**2[65,72]**	**272**	**8.6**	**3**	**2.8 (0.9 to 8.6)**	**0.06 (0.00 to 0.11)**	**18 (9 to 1000)**	**55 (1 to 110)**	**Low**
Clonidine	1[56]	57	3.5	0	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.13)			Insufficient

Bold - significant differences at 95% confidence level

Table 5. Adverse effects with antiepileptic drugs for migraine prevention in children

Adverse effect	Drug	RCTs Reference	Children	Rate with drug, %	Rate with placebo, %	Relative risk (95% CI)	Absolute risk difference (95% CI)	Number needed to treat to harm (95% CI)	Attributable events per 1000 treated (95% CI)
Any adverse event	**Divalproex sodium**	**2[63,75]**	**902**	**66.6**	**57.8**	**1.2 (1.0 to 1.3)**	**0.09 (0.03 to 0.16)**	**11 (6 to 34)**	**92 (29 to 155)**
Abdominal pain	Topiramate	2[65,73]	373	10.4	9.9	1.0 (0.6 to 1.9)	0.00 (-0.06 to 0.06)		
Anorexia	**Topiramate**	**4[62,65,72,73]**	**509**	**11.3**	**5.0**	**2.0 (1.0 to 3.9)**	**0.06 (0.01 to 0.11)**	**17 (10 to 83)**	**58 (12 to 105)**
Dizziness	Topiramate	3[65,72,73]	667	5.6	1.2	1.8 (0.3 to 10.2)	0.03 (-0.04 to 0.09)		
Fatigue	Topiramate	4[62,65,72,73]	509	6.9	7.8	0.8 (0.5 to 1.6)	-0.01 (-0.06 to 0.04)		
Injury	Topiramate	3[62,65,73]	373	8.1	8.6	0.9 (0.5 to 1.8)	0.00 (-0.06 to 0.06)		
Insomnia	Topiramate	2[65,72]	272	5.7	3.0	1.8 (0.5 to 6.2)	0.02 (-0.03 to 0.06)		
Nausea	Topiramate	2[62,65]	298	6.0	6.0	1.0 (0.4 to 2.6)	0.00 (-0.06 to 0.06)		
Nervousness	Topiramate	2[65,72]	272	4.3	0.0	3.7 (0.8 to 17.3)	0.04 (0.00 to 0.08)		
Paresthesia	**Topiramate**	**3[62,73]**	**373**	**14.5**	**5.3**	**2.6 (1.2 to 5.6)**	**0.09 (0.05 to 0.14)**	**11 (7 to 22)**	**92 (45 to 140)**
Pharyngitis	Topiramate	2[62,65]	298	8.8	13.8	0.6 (0.3 to 1.1)	-0.06 (-0.13 to 0.02)		
Sinusitis	Topiramate	3[62,65,73]	373	8.1	5.3	1.2 (0.5 to 2.5)	0.02 (-0.03 to 0.07)		
Somnolence	Topiramate	4[62,65,72,73]	373	7.7	3.9	1.6 (0.7 to 3.8)	0.04 (-0.01 to 0.09)		
Treatment discontinuation	Topiramate	4[62,65,72,73]	509	18.6	23.4	0.8 (0.6 to 1.1)	-0.04 (-0.11 to 0.03)		
Upper respiratory tract infection	**Topiramate**	**3[62,65,73]**	**373**	**21.7**	**11.2**	**1.8 (1.1 to 3.1)**	**0.11 (0.03 to 0.18)**	**10 (5 to 34)**	**105 (29 to 182)**
Weight decrease	**Topiramate**	**3[62,65,73]**	**373**	**20.8**	**12.5**	**2.0 (1.2 to 3.2)**	**0.09 (0.02 to 0.15)**	**11 (7 to 42)**	**87 (24 to 150)**

Bold - significant differences at 95% confidence level

Discussion

Migraine prevention in children was examined in 22 publications of 20 RCTs that enrolled 1,920 children. Only one drug, the beta blocker propranolol, prevented migraine more effectively than placebo (Table 6). Propranolol 60 to 120 mg/day resulted in complete cessation of migraine attacks in 713 per 1,000 treated children (95 percent CI, 452 to 974) (low strength of evidence from a single RCT).[55] The antiepileptic drugs clonidine, trazodone, and magnesium oxide failed to prevent migraine in children. Other antiepileptic drugs, including topiramate and divalproex sodium, not only failed to benefit children with migraine but also resulted in treatment discontinuation due to adverse effects (Table 4). Topiramate significantly increased risk of anorexia, weight decrease, paresthesia, and upper respiratory tract infection (Table 5).

No studies examined whether specific characteristics of children modify the effectiveness or safety with preventive drugs. Treatment effects may differ for children and adolescents. Published trials did not provide treatment effects among age subgroups.

Clinical decisions about drugs and nonpharmacological treatment for migraine prevention in children should include a careful estimation of the balance of benefits and harms. Our review confirmed previously published conclusions about the efficacy of propranolol for migraine prevention in children.[80] Nonpharmacological treatments demonstrated better benefit to harm ratios than drugs in head-to-head RCTs.[58, 70, 87] Individualized multimodal drug management showed promising results.[74] School-based psychological and drug management have both demonstrated positive results in treating acute headache attacks, but have yet to be examined for migraine prevention.[88, 89] RCTs have also not yet examined other drug management interventions, including integrated care, coordinated care, patient education, drug surveillance, and interactive drug monitoring.

The off-label antiepileptic drugs clonidine and trazodone failed to demonstrate efficacy for migraine prevention but resulted in bothersome adverse effects. Previously published reviews reported bothersome adverse effects with antiepileptic drugs in children with migraine[81, 82] or epilepsy.[83] Off-label use of the antidepressant trazodone in children with migraine was not effective. We could not conclude the effectiveness of other antidepressants for preventing migraine in children, nor could we determine whether adverse effects of antidepressants are similar when used for children with migraine compared to children with depression. We do know that antidepressants may increase risk of suicidal behavior in children and adolescents.[84] Use of off-label psychotropic drugs for migraine prevention could be justified in children with psychiatric comorbidity;[85] however, trials available for review did not report presence of comorbid illnesses in enrolled patients.

In fact, few available trials examined the seriousness or bothersomeness of harms with drugs. Clinicians considering off-label drugs for children with migraine must therefore base decisions on strong effectiveness evidence. Few clinical trials followed the recommendations from the Task Force on Adverse Events in Migraine Trials of the International Headache Society[86] when testing safety of the drugs in children.

Strength of evidence of drug benefits and harms was low in most cases due to risk of bias and imprecise estimates from underpowered RCTs. Reporting quality of trials was poor with few trials providing detailed information about prior or concomitant treatments, comorbidities, family history, socioeconomic status, drug overuse, and other important characteristics of children. On average, the trials lasted 20 weeks, and therefore did not provide sufficiently long-term evidence for benefits and harms with drugs that could be recommended for preventive use over very long time periods.

Our review has limitations. We did not conclude strength of evidence for flunarizine, which has been reported to be effective in preventing migraines in children, because this drug has not approved by the FDA. One low risk of bias Italian RCT suggested that flunarizine resulted in ≥50 percent reduction in migraine attacks in 500 children per 1,000 treated (95 percent CI, 260 to 740).[57] Our comprehensive literature search in several databases, trial registries, and the FDA reviews detected a very low publication rate of registered completed clinical trials involving children. We assume publication bias but did not contact the investigators of completed trials for unpublished data. We did request additional data from the sponsors of completed trials but received few responses. Thus, we know neither the results from unpublished trials nor how many unregistered studies have been conducted and never published. We relied on reported information and did not contact study authors for additional details about the trials, including design, execution, or poorly reported results that we could not reproduce.

Key Messages

Propranolol was more effective than placebo for preventing migraine in children, with no bothersome adverse effects that could lead to treatment discontinuation.

Antiepileptics were no more effective than placebo in preventing migraine but resulted in increased risk of treatment discontinuation due to adverse effects.

Internet-based self-management with multimodal CBT was better than education in preventing migraine in children and adolescents at 6 weeks but not at 6 months of followup.

Reporting quality of studies involving children is poor.

Our report offers insights for future research (Table 7). Future randomized trials should examine the comparative effectiveness of multimodal drug and disease management, long-term benefits, safety, and adherence with preventive treatments, and the role of specific characteristics of children that could modify benefits and harms with preventive drugs.

Randomized trials have examined few pharmacological agents, while practicing clinicians treat children with many off-label drugs; these should be formally tested. Large observational studies, including the American Migraine Prevalence and Prevention study, have relied on self-reported use of preventive medications without assessing exact drug use or effectiveness.[5] The few available studies of off-label drug use in children show that 5 percent of all prescribed antiepileptic drugs were prescribed for migraine.[90] European studies demonstrated that about 30 percent of children who are hospitalized[92] and 40 percent of children in outpatient settings received off-label drug prescriptions.[93]

European observational studies found significantly higher risk of adverse effects with off-label drugs, and concluded improper balance of benefits and risks with off-label drugs in pediatric patients.[93, 94]

Little is known about the use of off-label drugs for migraine prevention in children or about the comparative effectiveness of the drug classes used. Initial descriptive data could be culled from administrative databases. For example, analyses of Medicaid may shed light on practice patterns in migraine prevention and offer insight into the comparative effectiveness of preventive drugs on reducing visits to emergency rooms. Based on these analyses, RCTs could then be designed to examine the drugs for which the benefits and harms ratio was most favorable. Future studies should assess the efficacy and comparative effectiveness of multidisciplinary migraine drug management interventions based in the community, family, or school.

Trials should examine treatment effectiveness based on patient-centered outcomes, including: complete cessation of migraine attack or reduction in monthly migraine attacks by ≥50 percent, quality of life, migraine-related disability, and success with schooling. Researchers should use interaction models to examine how children's age, sex, race, ethnicity, and puberty affect the benefits and harms of preventive drugs. Studies should examine subgroups of children identified by age, sex, race, ethnicity, puberty, socioeconomic status, family history, and comorbid psychiatric conditions and other diseases. Studies should also examine the effectiveness and safety of preventive drugs and multidisciplinary interventions in children with chronic migraine, migraine with versus without aura, and those who failed previous preventive treatments.

Table 6. Evidence of migraine prevention in children

Outcome	Active	Control	RCTs Reference	Conclusion	Strength of evidence
Complete cessation of headache attacks	Propranolol	Placebo	1[55]	Propranolol was better than placebo in achieving complete cessation of migraine attacks.	Low
	Clonidine	Placebo	1[56]	Clonidine was not better than placebo in achieving complete cessation of migraine attacks.	Low
	Sodium valproate	Propranolol	2[67,68]	Sodium valproate and propranolol had no significant differences in complete cessation of headache attacks.	Low
Reduction by 50% in migraine attack frequency	Topiramate	Placebo	2[62,65]	Topiramate, 100-200 mg/day, did not increase rate of reduction in migraine by 50%.	Moderate
	Divalproex sodium	Placebo	1[63]	Divalproex sodium, 250-10 0mg/day did not increase rate of reduction in migraine by 50%.	Low
	Propranolol	Placebo	1[55]	Propranolol did not increase rate of reduction in migraine by 50%.	Low
	Clonidine	Placebo	1[56]	Clonidine did not increase rate of reduction in migraine by 50%.	Low
Reduction in frequency of migraine attack by ≥50% from baseline	Sodium valproate	Propranolol	2[67,68]	Sodium valproate and propranolol had no significant differences in reduction of migraine attack by ≥50% from baseline with both drugs.	Low
Reduction by 50% in migraine attack frequency	Metoprolol	Progressive relaxation training +stress management	1[70]		Low
	Metoprolol	Cephalic vasomotor feedback +stress management	1[70]	Metoprolol and cephalic vasomotor feedback + stress management had no significant differences in reduction of migraine attacks by ≥50%.	Low
	Applied relaxation	Educational intervention	1[74]	Applied relaxation and educational intervention had no significant differences in reduction of migraine attacks by 50%.	Low
	Multimodal CBT	Educational intervention	1[74]	Multimodal cognitive-behavioral training (CBT) was better than Educational intervention at 6 weeks but not 6 month in reduction of migraine attacks by 50%.	Low
	Multimodal CBT	Applied relaxation	1[74]	Multimodal CBT and applied relaxation had no significant differences in reduction of migraine attacks by 50%.	Low
Reduction for need for temporary drug therapy for single attacks	Clonidine	Placebo	1[56]	Clonidine did not decrease drug utilization for acute migraine attacks.	Low
Improvement in Pediatric Migraine Disability Assessment Score	Topiramate	Sodium valproate	1[69]	Topiramate and sodium valproate had no significant differences in Pediatric Migraine Disability Assessment Score.	Low

Table 7. Future research needs

Key question	Results of literature review	Types of studies needed to answer question	Future research recommendation
What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in children?	Only one drug, beta blocker propranolol prevented migraine more effectively than placebo in a single RCT. Multidisciplinary drug management including cognitive-behavioral training was more effective than usual care with educational intervention in preventing migraine in children and adolescents	Randomized trials; analysis of administrative databases to examine practice patterns of off label drug use and comparative effectiveness on health care utilization	Analyze efficacy of drugs that were effective for migraine prevention in children and adults: a. Beta blockers including -Propranolol -Timolol - Metoprolol - Atenolol - Nadolol - Pindolol - Bisoprolol - Nebivolol b. ACE inhibitor, Lisinopril c. Angiotensin II Antagonists including -Candesartan -Telmisartan Analyze efficacy and comparative effectiveness of multidisciplinary community, family, or school based migraine drug management interventions Analyze administrative databases (Medicaid, health insurance databases) to examine preventive drug utilization and effectiveness of preventive drugs on emergency room utilization. Trials should examine long-term treatment effectiveness based on patient centered outcomes including complete cessation of migraine attack or reduction in monthly migraine attacks by ≥50%; quality of life; migraine related disability; success with schooling.
What are the comparative harms from pharmacological treatments for preventing migraine attacks in children?	Topiramate and divalproex sodium resulted in treatment discontinuation due to adverse effects	Randomized trials; analysis of administrative databases; Case-series and case reports about harms with preventive drugs. Creation of the registry with adverse effects form preventive drugs in children with migraine	Analyze long-term safety of drugs with good benefits/harms profile in adults: a. Beta blockers b. ACE inhibitor, Lisinopril c. Angiotensin II Antagonists including -Candesartan -Telmisartan Analyze administrative databases (Medicaid, health insurance databases) to examine preventive drug utilization and comparative safety of preventive drugs on diagnosed adverse effects that lead to treatment discontinuation or additional health care utilization (emergency room visits, hospitalization)

Table 7. Future research needs (continued)

Key question	Results of literature review	Types of studies needed to answer question	Future research recommendation
Which characteristics of children predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks?	No studies examined how childrens' characteristics can improve effectiveness or safety of migraine preventive medications in children	Randomized trials; analysis of administrative databases	Examine with interaction models how children age, sex, race, ethnicity, puberty, socioeconomic status, family history, comorbid psychiatric and other diseases can modify benefits and harms with preventive drugs. Examine benefits and harms with preventive drugs in subgroups by children age, sex, race, ethnicity, puberty, socioeconomic status, family history, comorbid psychiatric and other diseases. Examine effectiveness and safety of preventive drugs and multidisciplinary interventions in children with chronic migraine, migraine with vs. without aura, and those who failed previous preventive treatments.

References

1. Goadsby PJ, Raskin NH. Chapter 15. Headache. In: Fauci AS, Braunwald E, Kasper DL, Hauser SL, Longo DL, Jameson JL, et al., eds. Harrison's principles of internal medicine. 17th ed. New York: The McGraw-Hill Companies; 2008.
2. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders: 2nd edition. Cephalalgia. 2004;24 Suppl 1:9-160. PMID: 14979299.
3. Silberstein SD. Preventive migraine treatment. Neurol Clin. 2009 May;27(2):429-43. PMID: 19289224.
4. Solomon GD, Santanello N. Impact of migraine and migraine therapy on productivity and quality of life. Neurology. 2000;55(9 Suppl 2):S29-35. PMID: 11089517.
5. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache. 2007 Mar;47(3):355-63. PMID: 17371352.
6. Lipton RB, Scher AI, Kolodner K, et al. Migraine in the United States: epidemiology and patterns of health care use. Neurology. 2002 Mar 26;58(6):885-94. PMID: 11914403.
7. Bigal ME, Lipton RB, Winner P, et al. Migraine in adolescents: association with socioeconomic status and family history. Neurology. 2007 Jul 3;69(1):16-25. PMID: 17606878.
8. Hernandez-Latorre MA, Roig M. Natural history of migraine in childhood. Cephalalgia. 2000 Jul;20(6):573-9. PMID: 11075841.
9. Lipton RB, Manack A, Ricci JA, et al. Prevalence and burden of chronic migraine in adolescents: results of the chronic daily headache in adolescents study (C-dAS). Headache. 2011 May;51(5):693-706. PMID: 21521206.
10. Lipton RB, Stewart WF, Diamond S, et al. Prevalence and burden of migraine in the United States: data from the American Migraine Study II. Headache. 2001 Jul-Aug;41(7):646-57. PMID: 11554952.
11. Sprenger T, Goadsby PJ. Migraine pathogenesis and state of pharmacological treatment options. BMC Medicine. 2009;7:71. PMID: 19917094.
12. Sanchez-Del-Rio M, Reuter U, Moskowitz MA. New insights into migraine pathophysiology. Curr Opin Neurol. 2006 Jun;19(3):294-8. PMID: 16702838.
13. Rapoport AM. Acute and prophylactic treatments for migraine: present and future. Neurol Sci. 2008 May;29 Suppl 1:S110-22. PMID: 18545911.
14. Stafford RS. Regulating off-label drug use--rethinking the role of the FDA. N Engl J Med. 2008 Apr 3;358(14):1427-9. PMID: 18385495.
15. Fraguas D, Merchan-Naranjo J, Laita P, et al. Metabolic and hormonal side effects in children and adolescents treated with second-generation antipsychotics. Journal of Clinical Psychiatry. 2008 Jul;69(7):1166-75. PMID: 18588363.
16. Correll CU, Carlson HE. Endocrine and metabolic adverse effects of psychotropic medications in children and adolescents. J Am Acad Child Adolesc Psychiatry. 2006 Jul;45(7):771-91. PMID: 16832314.
17. Pappagallo M, Silva R. The effect of atypical antipsychotic agents on prolactin levels in children and adolescents. J Child Adolesc Psychopharmacol. 2004 Fall;14(3):359-71. PMID: 15650493.
18. Kumra S, Oberstar JV, Sikich L, et al. Efficacy and tolerability of second-generation antipsychotics in children and adolescents with schizophrenia. Schizophr Bull. 2008 Jan;34(1):60-71. PMID: 17923452.
19. Dubois D. Toxicology and overdose of atypical antipsychotic medications in children: does newer necessarily mean safer? Curr Opin Pediatr. 2005 Apr;17(2):227-33. PMID: 15800418.
20. Silberstein S, Tfelt-Hansen P, Dodick DW, et al. Guidelines for controlled trials of prophylactic treatment of chronic migraine in adults. Cephalalgia. 2008 May;28(5):484-95. PMID: 18294250.
21. Schroeder BM. AAFP/ACP-ASIM release guidelines on the management and prevention of migraines. Am Fam Physician. 2003 Mar 15;67(6):1392, 5-7. PMID: 12674472.
22. Olesen J, Bousser MG, Diener HC, et al. New appendix criteria open for a broader concept of chronic migraine. Cephalalgia. 2006 Jun;26(6):742-6. PMID: 16686915.
23. Lewis D, Ashwal S, Hershey A, et al. Practice parameter: pharmacological treatment of migraine headache in children and adolescents: report of the American Academy of Neurology Quality Standards Subcommittee and the Practice Committee of the Child Neurology Society. Neurology. 2004 Dec 28;63(12):2215-24. PMID: 15623677.

24. Gunner KB, Smith HD, Ferguson LE. Practice guideline for diagnosis and management of migraine headaches in children and adolescents: Part two. J Pediatr Health Care. 2008 Jan-Feb;22(1):52-9. PMID: 18174091.
25. Geraud G, Lanteri-Minet M, Lucas C, et al. French guidelines for the diagnosis and management of migraine in adults and children. Clin Ther. 2004 Aug;26(8):1305-18. PMID: 15476911.
26. Evers S, Afra J, Frese A, et al. EFNS guideline on the drug treatment of migraine--revised report of an EFNS task force. Eur J Neurol. 2009 Sep;16(9):968-81. PMID: 19708964.
27. Dowson AJ, Lipscombe S, Sender J, et al. New guidelines for the management of migraine in primary care. Curr Med Res Opin. 2002;18(7):414-39. PMID: 12487508.
28. Morey SS. Guidelines on migraine: part 4. General principles of preventive therapy. Am Fam Physician. 2000 2000 Nov 15;62(10):2359-60. PMID: 11126860.
29. Silberstein SD. Practice parameter: evidence-based guidelines for migraine headache (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. Neurology. 2000 Sep 26;55(6):754-62. PMID: 10993991.
30. Schuurmans A, van Weel C. Pharmacologic treatment of migraine. Comparison of guidelines. Can Fam Physician. 2005 Jun;51:838-43. PMID: 15986940.
31. Whitlock EP, Lopez SA, Chang S, et al. AHRQ series paper 3: identifying, selecting, and refining topics for comparative effectiveness systematic reviews: AHRQ and the effective health-care program. J Clin Epidemiol. 2010 May;63(5):491-501. PMID: 19540721.
32. Slutsky J, Atkins D, Chang S, et al. Comparing medical interventions: AHRQ and the Effective Health Care Program. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. 2011/03/25 ed. Vol. March 2011. Rockville, MD: Agency for Healthcare Research and Quality; 2008:1-4. Available at www.effectivehealthcare.ahrq.gov.
33. Helfand M, Balshem H. Principles in Developing and Applying Guidance. 2008PMID: 21433405.
34. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Annals of Internal Medicine. 2009 Aug 18;151(4):W65-94. PMID: 19622512.
35. Norris S, Atkins D, Bruening W, et al. Chapter 4. Selecting observational studies for comparing medical interventions. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:56-68. Available at: www.effectivehealthcare.ahrq.gov.
36. Higgins J, Green S, eds. Cochrane handbook for systematic reviews of interventions. Version 5.1.0. London: The Cochrane Collaboration; 2011.
37. Chou R, Aronson N, Atkins D, et al. AHRQ series paper 4: assessing harms when comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2008 Sep 25;63(5):502-12. PMID: 18823754.
38. Rothner AD. Complicated migraine and migraine variants. Curr Pain Headache Rep. 2002 Jun;6(3):233-9. PMID: 12003695.
39. Hansen JM, Thomsen LL, Olesen J, et al. Calcitonin gene-related peptide does not cause the familial hemiplegic migraine phenotype. Neurology. 2008 Sep 9;71(11):841-7. PMID: 18779512.
40. Higgins JP, Altman DG, Gotzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928. PMID: 22008217.
41. Viswanathan M, Berkman ND. Development of the RTI Item Bank on Risk of Bias and Precision of Observational Studies AHRQ Methods for Effective Health Care. 2011 Sep Studies;Rockville (MD): Agency for Healthcare Research and Quality (US)(Report No.: 11-EHC028-EF)PMID: 22191112.
42. Owens DK, Lohr KN, Atkins D, et al. AHRQ series paper 5: grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):513-23. PMID: 19595577.
43. Guyatt G, Oxman AD, Kunz R, et al. GRADE guidelines 6. Rating the quality of evidence-imprecision. J Clin Epidemiol. 2011 Aug 10PMID: 21839614.
44. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. BMJ. 2011;343:d4002. PMID: 21784880.
45. Aschengrau A, Seage GR. Essentials of epidemiology in public health. Sudbury, MA: Jones and Bartlett; 2003.

46. van der Velde G, van Tulder M, Cote P, et al. The sensitivity of review results to methods used to appraise and incorporate trial quality into data synthesis. Spine (Phila Pa 1976). 2007 Apr 1;32(7):796-806. PMID: 17414916.
47. Herbison P, Hay-Smith J, Gillespie WJ. Adjustment of meta-analyses on the basis of quality scores should be abandoned. J Clin Epidemiol. 2006 Dec;59(12):1249-56. PMID: 17098567.
48. Wallace BC, Schmid CH, Lau J, et al. Meta-Analyst: software for meta-analysis of binary, continuous and diagnostic data. BMC Med Res Methodol. 2009;9:80. PMID: 19961608.
49. Egger M, Smith GD, Altman DG. Systematic reviews in health care: meta-analysis in context. 2nd ed. London: BMJ Books; 2001.
50. Viechtbauer W. Confidence intervals for the amount of heterogeneity in meta-analysis. Stat Med. 2007 Jan 15;26(1):37-52. PMID: 16463355.
51. Knapp G, Biggerstaff BJ, Hartung J. Assessing the amount of heterogeneity in random-effects meta-analysis. Biom J. 2006 Apr;48(2):271-85. PMID: 16708778.
52. Fu R, Gartlehner G, Grant M, et al. Chapter 9. Conducting quantitative synthesis when comparing medical interventions. Methods Guide for Effectiveness and Comparative Effectiveness Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Research and Quality. March 2011:104-19. Available at: http://effectivehealthcare.ahrq.gov.
53. Ebrahim S. The use of numbers needed to treat derived from systematic reviews and meta-analysis. Caveats and pitfalls. Eval Health Prof. 2001 Jun;24(2):152-64. PMID: 11523384.
54. Altman DG. Confidence intervals for the number needed to treat. BMJ. 1998 Nov 7;317(7168):1309-12. PMID: 9804726.
55. Ludvigsson J. Propranolol used in prophylaxis of migraine in children. Acta neurologica Scandinavica; 1974. p. 109-15.
56. Sillanpää M. Clonidine prophylaxis of childhood migraine and other vascular headache. A double blind study of 57 children. Headache; 1977. p. 28-31.
57. Sorge F, Marano E. Flunarizine v. placebo in childhood migraine. A double-blind study. Cephalalgia. 1985 May;5 Suppl 2:145-8. PMID: 2861907.
58. Olness K, MacDonald JT, Uden DL. Comparison of self-hypnosis and propranolol in the treatment of juvenile classic migraine. Pediatrics. 1987 Apr;79(4):593-7. PMID: 3822681.
59. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache. 1990 Apr;30(5):264-8. PMID: 2191938.
60. Battistella PA, Ruffilli R, Moro R, et al. A placebo-controlled crossover trial of nimodipine in pediatric migraine. Headache; 1990. p. 264-8.
61. Battistella PA, Ruffilli R, Cernetti R, et al. A placebo-controlled crossover trial using trazodone in pediatric migraine. Headache. 1993 Jan;33(1):36-9. PMID: 8436497.
62. Winner P, Pearlman EM, Linder SL, et al. Topiramate for migraine prevention in children: a randomized, double-blind, placebo-controlled trial. Headache. 2005 Nov-Dec;45(10):1304-12. PMID: 16324162.
63. Apostol G, Cady RK, Laforet GA, et al. Divalproex extended-release in adolescent migraine prophylaxis: results of a randomized, double-blind, placebo-controlled study. Headache. 2008 Jul;48(7):1012-25. PMID: 18705027.
64. Sheridan PH. Clinical Review. 2008:1-59. PMID: NDA 21168: M02-488.
65. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics. 2009 Mar;123(3):924-34. PMID: 19255022.
66. Wang F, Van Den Eeden SK, Ackerson LM, et al. Oral magnesium oxide prophylaxis of frequent migrainous headache in children: a randomized, double-blind, placebo-controlled trial. Headache. 2003 Jun;43(6):601-10. PMID: 12786918.
67. Ashrafi MR, Shabanian R, Zamani GR, et al. Sodium Valproate versus Propranolol in paediatric migraine prophylaxis. Eur J Paediatr Neurol. 2005;9(5):333-8. PMID: 16120482.
68. Bidabadi E, Mashouf M. A randomized trial of propranolol versus sodium valproate for the prophylaxis of migraine in pediatric patients. Paediatric Drugs. 2010 Aug 1;12(4):269-75. PMID: 20593910.
69. Unalp A, Uran N, Ozturk A. Comparison of the effectiveness of topiramate and sodium valproate in pediatric migraine. J Child Neurol. 2008 Dec;23(12):1377-81. PMID: 19073842.

70. Sartory G, Muller B, Metsch J, et al. A comparison of psychological and pharmacological treatment of pediatric migraine. Behav Res Ther. 1998 Dec;36(12):1155-70. PMID: 9745800.
71. Lewis D, Paradiso E. A double-blind, dose comparison study of topiramate for prophylaxis of basilar-type migraine in children: a pilot study. Headache. 2007 Nov-Dec;47(10):1409-17. PMID: 18052950.
72. Pandina GJ, Ness S, Polverejan E, et al. Cognitive effects of topiramate in migraine patients aged 12 through 17 years. Pediatr Neurol. 2010 Mar;42(3):187-95. PMID: 20159428.
73. Winner P, Gendolla A, Stayer C, et al. Topiramate for migraine prevention in adolescents: a pooled analysis of efficacy and safety. Headache. 2006 Nov-Dec;46(10):1503-10. PMID: 17115983.
74. Trautmann E, Kroner-Herwig B. A randomized controlled trial of Internet-based self-help training for recurrent headache in childhood and adolescence. Behav Res Ther. 2010 Jan;48(1):28-37. PMID: 19782343.
75. Sorge F, De Simone R, Marano E, et al. Flunarizine in prophylaxis of childhood migraine. A double-blind, placebo-controlled, crossover study. Cephalalgia. 1988 Mar;8(1):1-6. PMID: 3282670.
76. Freitag FG. Topiramate prophylaxis in patients suffering from migraine with aura: results from a randomized, double-blind, placebo-controlled trial. Advanced Studies in Medicine; 2003. p. S562-s4.
77. Cruz MJ, Valencia I, Legido A, et al. Efficacy and tolerability of topiramate in pediatric migraine. Pediatric Neurology. 2009 Sep;41(3):167-70. PMID: 19664530.
78. Apostol G, Lewis DW, Laforet GA, et al. Divalproex sodium extended-release for the prophylaxis of migraine headache in adolescents: results of a stand-alone, long-term open-label safety study. Headache. 2009 Jan;49(1):45-53. PMID: 19040679.
79. Pakalnis A, Greenberg G, Drake ME, Jr., et al. Pediatric migraine prophylaxis with divalproex. Journal of Child Neurology. 2001 Oct;16(10):731-4. PMID: 11669346.
80. Victor S, Ryan SW. Drugs for preventing migraine headaches in children. Cochrane Database of Systematic Reviews. 2003(4):CD002761. PMID: 14583952.
81. Jayapal S, Maheshwari N. Question 3. Topiramate for chronic migraine in children. Arch Dis Child. 2011 Mar;96(3):318-21. PMID: 21317129.
82. Damen L, Bruijn J, Verhagen AP, et al. Prophylactic treatment of migraine in children. Part 2. A systematic review of pharmacological trials. Cephalalgia. 2006 May;26(5):497-505. PMID: 16674757.
83. Connock M, Frew E, Evans BW, et al. The clinical effectiveness and cost-effectiveness of newer drugs for children with epilepsy. A systematic review. Health Technol Assess. 2006 Mar;10(7):iii, ix-118. PMID: 16545206.
84. Bridge JA, Iyengar S, Salary CB, et al. Clinical response and risk for reported suicidal ideation and suicide attempts in pediatric antidepressant treatment: a meta-analysis of randomized controlled trials. JAMA. 2007 Apr 18;297(15):1683-96. PMID: 17440145.
85. Breslau N. Psychiatric comorbidity in migraine. Cephalalgia. 1998 Aug;18 Suppl 22:56-8; discussion 8-61. PMID: 9793713.
86. Tfelt-Hansen P, Bjarnason NH, Dahl, et al. Evaluation and registration of adverse events in clinical drug trials in migraine. Cephalalgia. 2008 Jul;28(7):683-8. PMID: 18498392.
87. Damen L, Bruijn J, Koes BW, et al. Prophylactic treatment of migraine in children. Part 1. A systematic review of non-pharmacological trials. Cephalalgia. 2006 Apr;26(4):373-83. PMID: 16556238.
88. Larsson B, Carlsson J, Fichtel A, et al. Relaxation treatment of adolescent headache sufferers: results from a school-based replication series. Headache. 2005 Jun;45(6):692-704. PMID: 15953302.
89. Fichtel A, Larsson B. Relaxation treatment administered by school nurses to adolescents with recurrent headaches. Headache. 2004 Jun;44(6):545-54. PMID: 15186298.
90. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005--a study from the Netherlands. Eur J Clin Pharmacol. 2008 Oct;64(10):1013-20. PMID: 18618103.
91. Bazzano AT, Mangione-Smith R, Schonlau M, et al. Off-label prescribing to children in the United States outpatient setting. Acad Pediatr. 2009 Mar-Apr;9(2):81-8. PMID: 19329098.
92. Choonara I, Conroy S. Unlicensed and off-label drug use in children: implications for safety. Drug Safety. 2002;25(1):1-5. PMID: 11820908.

93. Horen B, Montastruc JL, Lapeyre-Mestre M. Adverse drug reactions and off-label drug use in paediatric outpatients. Br J Clin Pharmacol. 2002 Dec;54(6):665-70. PMID: 12492616.
94. Ufer M, Kimland E, Bergman U. Adverse drug reactions and off-label prescribing for paediatric outpatients: a one-year survey of spontaneous reports in Sweden. Pharmacoepidemiol Drug Saf. 2004 Mar;13(3):147-52. PMID: 15072113.
95. Bille B. A 40-year follow-up of school children with migraine. Cephalalgia. 1997 Jun;17(4):488-91; discussion 7. PMID: 9209767.
96. Guidetti V, Galli F. Evolution of headache in childhood and adolescence: an 8-year follow-up. Cephalalgia. 1998 Sep;18(7):449-54. PMID: 9793696.
97. Damen L, Bruijn JK, Verhagen AP, et al. Symptomatic treatment of migraine in children: a systematic review of medication trials. Pediatrics. 2005 Aug;116(2):e295-302. PMID: 16061583.
98. Solomon S. New appendix criteria open for a broader concept of chronic migraine (Comment on: Cephalagia 2006 Jun:26(6):742-6). Cephalalgia. 2007 May;27(5):469; author reply -70. PMID: 17448186.
99. U.S. Food and Drug Administration. FDA News Release: FDA Approves Botox to Treat Chronic Migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.
100. White CM, Ip S, McPheeters ML, et al. Chapter 11. Using existing systematic reviews to replace de novo processes in conducting comparative effectiveness reviews. Methods Guide for Effectiveness and Comparative Reviews. AHRQ Publication No. 10(11)-EHC063-EF. Rockville, MD: Agency for Healthcare Resarch and Quality: March 2011; 2009:136-51. Available at www.effectivehealthcare.ahrq.gov.
101. Slutsky J, Atkins D, Chang S, et al. AHRQ series paper 1: comparing medical interventions: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):481-3. PMID: 18834715.
102. Helfand M, Balshem H. AHRQ series paper 2: principles for developing guidance: AHRQ and the Effective Health-Care Program. J Clin Epidemiol. 2010 May;63(5):484-90. PMID: 19716268.
103. Harris RP, Helfand M, Woolf SH, et al. Current methods of the US Preventive Services Task Force: a review of the process. Am J Prev Med. 2001 Apr;20(3 Suppl):21-35. PMID: 11306229.
104. Rucker G, Schwarzer G, Carpenter J, et al. Why add anything to nothing? The arcsine difference as a measure of treatment effect in meta-analysis with zero cells. Stat Med. 2009 Feb 28;28(5):721-38. PMID: 19072749.
105. Bradburn MJ, Deeks JJ, Berlin JA, et al. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. Stat Med. 2007 Jan 15;26(1):53-77. PMID: 16596572.
106. Sweeting MJ, Sutton AJ, Lambert PC. What to add to nothing? Use and avoidance of continuity corrections in meta-analysis of sparse data. Stat Med. 2004 May 15;23(9):1351-75. PMID: 15116347.
107. Stijnen T, Hamza TH, Ozdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. Stat Med. 2010 Dec 20;29(29):3046-67. PMID: 20827667.
108. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177-88. PMID: 3802833.
109. U.S. Food and Drug Administration. Clinical Review of Divalproex Sodium. 2008.
110. Jurgens TP, Ihle K, Stork JH, et al. "Alice in Wonderland syndrome" associated with topiramate for migraine prevention. J Neurol Neurosurg Psychiatry. 2011 Feb;82(2):228-9. PMID: 20571045.
111. Sorge F, Barone P, Steardo L. Amitriptyline as a prophylactic for migraine in children. Acta Neurologica. 1982;4(5):362-7.
112. Sills M, Congdon P, Forsythe I. Clonidine and childhood migraine: a pilot and double-blind study. Dev Med Child Neurol. 1982 Dec;24(6):837-41. PMID: 6218003.
113. Chan VW, McCabe EJ, MacGregor DL. Botox treatment for migraine and chronic daily headache in adolescents. Journal of Neuroscience Nursing. 2009 Oct;41(5):235-43. PMID: 19835236.

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
ARD	Absolute risk difference
CBT	Cognitive behavioral training
CI	Confidence interval
FDA	Food and Drug Administration
MeSH	Medical Subject Heading
PICOTS	Population, Intervention, Comparator, Outcome, Timing, and Setting
PRISMA	Preferred Reporting Items for Systematic Review and Meta-Analysis
RCT	Randomized controlled trial