Effective Health Care Program

Comparative Effectiveness Review
Number 103

Migraine in Adults: Preventive Pharmacologic Treatments

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Migraine in Adults: Preventive Pharmacologic Treatments

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Prepared by:
Minnesota Evidence-based Practice Center
Minneapolis, MN

Investigators:
Tatyana A. Shamliyan, M.D., M.S.
Robert L. Kane, M.D.
Frederick R. Taylor, M.D.

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. These reviews provide comprehensive, science-based information on common, costly medical conditions, and new health care technologies and strategies.

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 can help clarify whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about AHRQ EPC systematic reviews, see www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that these systematic reviews will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email list to learn about new program products and opportunities for input.

We welcome comments on this systematic review. 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 email 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

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Key Informants

In designing the study questions, the EPC consulted several Key Informants who represent the end-users of research. The EPC sought the Key Informant input on the priority areas for research and synthesis. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their role as end-users, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who participated in developing this report follows:

Thomas Becker, M.D., M.B.A.
Medica Health Plans
Minnetonka, MN

Roger K. Cady, M.D.
Headache Care Center
Springfield, MO

Robert Dalton
National Headache Foundation
Chicago, IL

Lida Etermad, Pharm.D., M.S.
United Healthcare
Edina, MN

Andrew D. Hershey, M.D., Ph.D.
University of Cincinnati College of Medicine
Cincinnati, OH

Brady Patrick-Lake, M.F.S.
Consumer representative
Erie, CO

Alan M. Rapoport, M.D.
David Geffen School of Medicine, UCLA
Los Angeles, CA

Stephen D. Silberstein, M.D., FACP
Jefferson Headache Center
Philadelphia, PA

Technical Expert Panel

In designing the study questions and methodology at the outset of this report, the EPC consulted several technical and content experts. Broad expertise and perspectives were sought. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore, in the end, study questions, design, methodologic approaches, and/or conclusions do not necessarily represent the views of individual technical and content experts.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

The list of Technical Experts who participated in developing this report follows:

Andrew Blumenfeld, M.D.
Kaiser Permanente
San Diego, CA

Roger K. Cady, M.D.
Headache Care Center
Springfield, MO

Andrew D. Hershey, M.D., Ph.D.
University of Cincinnati College of Medicine
Cincinnati, OH

Alan M. Rapoport, M.D.
David Geffen School of Medicine, UCLA
Los Angeles, CA

Stephen D. Silberstein, M.D., FACP
Jefferson Headache Center
Philadelphia, PA

Peer Reviewers

Prior to publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report does not necessarily represent the views of individual reviewers.

Peer Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals with potential nonfinancial conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential nonfinancial conflicts of interest identified.

The list of Peer Reviewers follows:

Andrew Blumenfeld, M.D.
Kaiser Permanente
San Diego, CA

Frederick Freitag, D.O., FAHS
Baylor Research Institute
Dallas, TX

Rochelle Fu, Ph.D.
Oregon Evidence-based Practice Center
Portland, OR

Bray Patrick-Lake, M.F.S.
Consumer representative
Erie, CO

Structured Abstract

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

Data sources. We searched major electronic bibliographic databases and trial registries up to May 20, 2012.

Review methods. We performed a systematic review of published, English-language original studies of pharmacologic treatments for prevention of episodic or chronic migraine. Studies that compared drugs with inactive controls, nonpharmacologic interventions, or other drugs were eligible. Outcomes evaluated included rates of complete migraine cessation, ≥50 percent reduction in monthly migraine frequency, reduction in migraine-related disability, and improvement in quality of life. 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 participants treated.

Results. Of 5,244 retrieved references, 245 publications of randomized controlled clinical trials (RCTs) and 76 publications of nonrandomized therapeutic studies met eligibility criteria. Most enrollees were middle-aged Caucasian women, with an average of five monthly migraine attacks. Few trials reported the proportion of obese subjects, but many subjects were overweight. More than half of the RCTs defined migraine according to the International Headache Society criteria. 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.

For chronic migraine, botulinum toxin formulations were examined in 20 RCTs of 4,237 adults. Onabotulinumtoxin A was more effective than placebo in reducing monthly chronic migraine attacks by ≥50 percent (low-strength evidence from 3 RCTs of 459 adults) with inconsistent improvement in quality of life. Pooled analyses demonstrated that per 1,000 treated adults, 170 (95% confidence interval [CI], 82 to 258) would experience ≥50 percent reduction in migraine frequency, 155 (95% CI, 90 to 220) would experience adverse effects, and 26 (95% CI, 10 to 43) would discontinue treatments due to bothersome adverse effects. Topiramate reduced disability in patients with chronic migraine but failed to decrease monthly migraine frequency by ≥50 percent (low-strength evidence from one RCT of 328 adults). Individual RCTs examined the comparative effectiveness of onabotulinumtoxin A with topiramate or divalproex and found no differences in chronic migraine prevention. Propranolol combined with topiramate treatment demonstrated no benefits in nonresponders to topiramate monotherapy (low-strength evidence from one RCT of 191 adults).

For episodic migraine, RCTs examined 59 drugs from 14 drug classes. All approved drugs (topiramate, divalproex, timolol, and propranolol), some 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 would result in clinical improvement in 200 to 400 patients per 1,000 treated. Adverse effects leading to treatment discontinuation were examined in 68 RCTs. Topiramate, off-label antiepileptics, and

antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.

Limited direct evidence of comparative effectiveness from head-to-head RCTs demonstrated no consistent significant differences in outcomes with examined drugs in patients with episodic migraine. Exploratory indirect adjusted frequentist analysis offered low-strength evidence that the angiotensin II receptor blocker candesartan was more effective than approved drugs including topiramate, propranolol, timolol, and divalproex. Exploratory network Bayesian meta-analysis offered low-strength evidence that angiotensin inhibiting drugs (captopril, lisinopril, candesartan) were the most effective and tolerable for episodic migraine prevention in adults who have no contraindications to examined drugs.

Individual RCTs of drug-management interventions for episodic migraine offered low-strength evidence that compared with 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 drugs.

Conclusions. For chronic migraine, onabotulinumtoxin A reduced migraine attacks but increased the risk of adverse effects and treatment discontinuation due to adverse effects. For episodic migraine, approved drugs are effective but increase risk of adverse effects and treatment discontinuation due to adverse effects. Some off-label beta blockers and angiotensin inhibiting drugs are effective without bothersome harms and therefore offer the best benefits-to-harms ratio. We could not determine the long-term (i.e., trials of more than 3 months' duration), preventive benefits and adherence with drugs. 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.

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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] Episodic migraine affects 17 percent of women and 6 percent of men.[5-8]

Migraine frequency is divided into episodic and chronic.[2] Episodic migraine is characterized by <15 migraine days 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 1.4 to 2.2 percent of adults.[9] 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.[10]

Forty percent of adults with episodic migraine and all patients with chronic migraine might benefit from preventive medication; yet, only about 12 percent of adults with frequent migraines take preventive medication.[5] Preventive medications from several drug classes are thought to affect various aspects of migraine pathophysiology.[11,12] The U.S. Food and Drug Administration (FDA) has approved four drugs for *episodic* migraine prevention in adults: the beta blockers propranolol and timolol, and the antiepileptic drugs topiramate and divalproex sodium.[13] For prevention of *chronic* migraine, the FDA has approved only one drug, onabotulinumtoxin A. Doctors also prescribe off-label drugs (approved for clinical conditions other than migraine prevention), including novel antiepileptic drugs, calcium channel blockers, serotonin and noradrenaline reuptake inhibitors, glutamate blockers, and drugs from several other classes.[13]

Preventive treatments aim to eliminate headache pain without intolerable harms. Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of ≥50 percent.[3] Preventive treatments are also expected to reduce use of acute drugs and improve quality of life.[6] Treatment safety is defined by the total rates of adverse effects and 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.[14,15] Drug choices in clinical practice are based on many drug-related factors such as familiarity, efficacy, and adverse effects, as well as many patient characteristics such as headache frequency, presence of aura, comorbid conditions, and patient preference.

Indications for preventive treatments differ. The American Migraine Prevalence and Prevention expert advisory group recommends preventive treatment for those who experience two or more monthly headache attacks accompanied by disability, and for those who experience four or more monthly attacks with or without accompanying disability.[16] Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month, but others suggest it only for those who experience a headache on most days of the month.[17,18] Often, preventive treatment is recommended for only 6 to 9 months; however, very limited research has examined migraine frequency after discontinuation of preventive treatments.[3,19]

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 pharmacologic and nonpharmacologic treatments.[20] 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.[20,21]

Scope

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

During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of neurology, primary care, consumers, scientific experts, and payers, to help define the Key Questions (KQs).[22] The KQs were then posted for public comment for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access from April 12, 2012, to May 10, 2012, at the AHRQ Effective Health Care Web site.

We chose not to synthesize studies of the drug flunarizine, which is commonly used for adults in Europe, because the FDA has not approved it. Efficacy of nonpharmacologic preventive treatments was beyond our scope. We conducted a comprehensive literature review following the principles in the "Methods Guide for Effectiveness and Comparative Effectiveness Reviews" (hereafter the Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program[23,24] and PRISMA guidelines (protocol registration number is CRD42012001918, available at www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42012001918).

Key Questions

KQ 1

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

a. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with placebo or no active treatment?
b. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active pharmacologic treatments?
c. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?
d. How do preventive pharmacologic treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic 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?

KQ 2

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

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

KQ 3

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

Methods

We followed an a priori research protocol that we developed with the clinical and methodological input of a technical expert panel. The protocol followed the Effective Health Care Program's Methods Guide.

Literature 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 May 20, 2012. To search the grey literature, we accessed the FDA Web site to find medical and statistical reviews of the eligible drugs and we searched several trial registries to find ongoing, completed, and published trials of migraine prevention.

Eligibility

Three investigators independently determined study eligibility, resolving disagreements through discussions until consensus was achieved.[25] To assess the effectiveness of drugs, we analyzed all included RCTs. To assess adverse effects and treatment discontinuation due to adverse effects, we analyzed all included RCTs and nonrandomized studies.[26] We defined harms as the totality of all possible adverse consequences of an intervention.[27] We analyzed harms regardless of how authors perceived causality of treatments.

We determined eligibility according to the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, and Settings) framework. We defined the target population as community-dwelling adults with episodic or chronic migraine. We formulated a list of eligible interventions after discussions with key informants and technical experts and after consideration of public comments. Eligible comparators included pharmacologic, nonpharmacologic, and combined

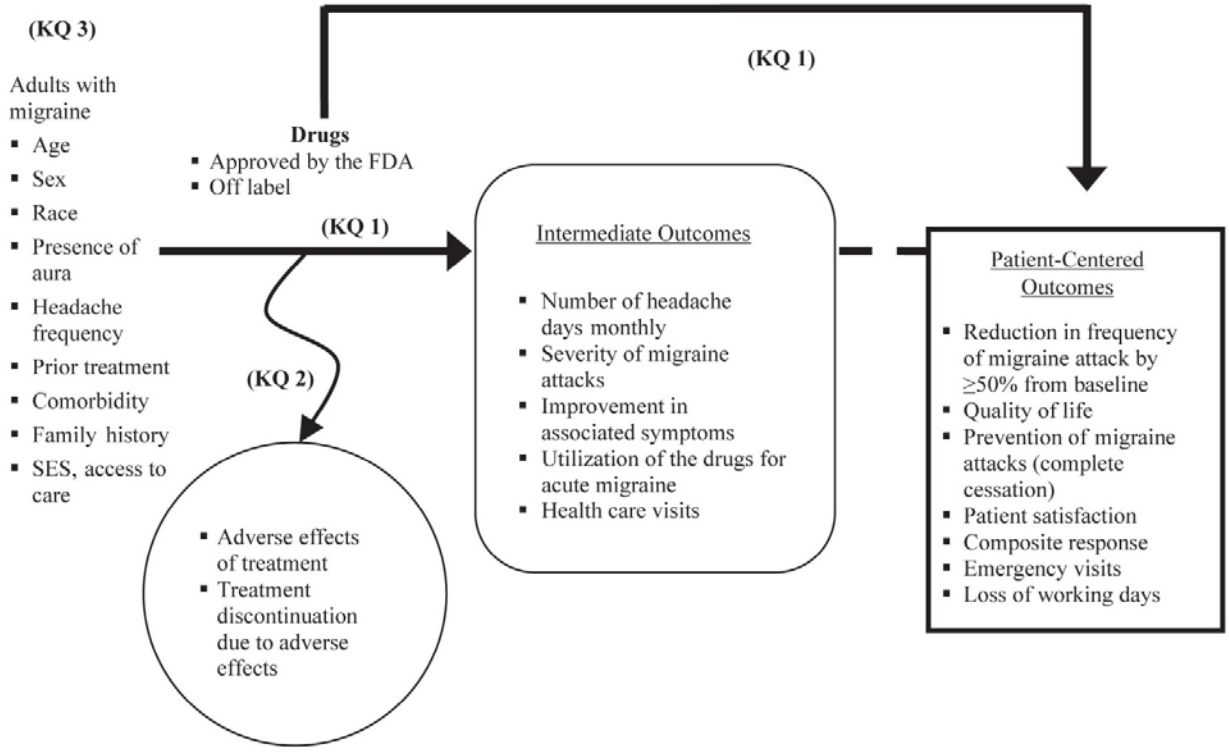
preventive treatments. We defined eligible intermediate and patient-centered outcomes (presented in the analytical framework, Figure A).

Eligible studies included patients with episodic migraine, chronic daily headache, or chronic migraine defined according to the criteria of the International Headache Society.[17] 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. We also excluded studies of short-term prevention of migraine, including menstrual migraines.

Data Extraction

Researchers used standardized forms to extract data (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy). For each trial, one reviewer extracted the data 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.

Figure A. Analytical framework



KQ = Key Question; SES = socioeconomic status
KQ 1: What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in adults?
KQ 2: What are the comparative harms from pharmacologic treatments for preventing migraine attacks in adults?
KQ 3: Which patient characteristics predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks in adults?

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% confidence interval (CI).

We abstracted the number randomized to each treatment group as the denominator to calculate estimates by applying intention-to-treat principles assuming that the same proportions apply in the missing data. We abstracted drug regimen and doses and patient characteristics including demographics, baseline frequency and severity, and prior treatment status as factors that can modify treatment effects. We abstracted sponsorship of the studies and conflict of interest by the authors. 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.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies for benefits and harms using the criteria from the Cochrane risk of bias tool.[28] We evaluated: (1) random allocation of the subjects to the treatment groups; (2) masking of the treatment status to the participants and investigators; (3) adequacy of allocation concealment; (4) adequacy of randomization as estimated based on similarity of the subjects in treatment groups by demographics and by frequency and severity of migraine; (5) use of planned and executed intention-to-treat principles; and (6) selective outcome reporting when compared with the protocols (when available) and methods sections in the articles. Since all outcomes in the review were self-reported, masking of outcome assessment was not essential.

We assumed a low risk of bias when RCTs met all of the risk of bias criteria, a medium 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 adjustment for confounding factors to address selection bias and exclusion of subjects from the analyses to address 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.

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 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.[17] Thus, eligible studies published before 2004 defined classic or common migraine as per previous definitions from the International Headache Society or the Ad Hoc Committee on Classification of Headache.[29] We compared baseline patient characteristics and treatment effects depending on the exact migraine definition and report the results when they are significantly different.

Using Meta-Analyst and STATA® software, 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 evaluated statistical significance at a 95 percent confidence level. We used default software continuity coefficients for 0 events and intention to treat as recommended calculations for missing data. We hypothesized superiority of drugs versus placebo and versus each other.

For pooling results from studies addressing KQs 1 and 2, we required that studies included the same active drug treatments and comparators and the same definitions of the outcomes. Cohen standardized mean differences were calculated for different continuous measures of the same outcome. For sparse adverse effects data, we used multiple models to test robustness of inferential statistics.

We tested consistency in the results by comparing the direction and strength of the association and assessed heterogeneity in results with chi-squared and I-squared tests. We explored heterogeneity with meta-regression and sensitivity analysis, reporting only the results from random effects models. 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. 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.

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

In cases when very few studies were available to provide evidence from direct head-to-head comparisons, we conducted indirect comparisons. To do so, we used statistical techniques to estimate the treatment effects from studies of each given treatment against controls under an assumption of consistency.

- We used adjusted indirect frequentist comparisons for individual drugs that were compared with placebo. This analysis provided pair-wise triangular comparisons for drugs that were compared against placebo rather than network meta-analysis.
- To address the problems with inevitable differences across studies, we used mixed (or multiple) treatment comparisons (MTCs), or so-called Bayesian network meta-analysis. We calculated Bayesian odds ratios with 2.5 to 97.5 percent credible intervals and Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments. We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class demonstrated no significant differences in outcomes. We concluded no differences in drug effect (hereafter called similar effects) if confidence or credible intervals included one (no effect or no difference). All Bayesian

results were obtained from the WinBUGS software using Markov chain Monte Carlo (MCMC) samples after a 50,000-sample algorithm burn-in.

Grading the Evidence for Each KQ

We assessed strength of evidence according to risk of bias, consistency, directness, and precision for each patient-centered outcome, which included 100 percent or ≥50 percent reduction in monthly migraine frequency, patient global assessment of treatment success, rates of clinically important improvement in migraine-related disability and quality of life.[30] We also assessed treatment discontinuation due to harms. We based our criteria on published guidelines acknowledging inevitable subjectivity of the assessment. We assigned a medium or high risk of bias in the body of evidence when at least one individual RCT had medium or high risk of bias, respectively.We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95% CIs, and the pooled sample had ≥300 events (using 25% relative effect difference for calculation of optimal information size).[31] We did not include justification of the sample size into grading of the evidence nor did we conduct post hoc statistical power analysis.

As part of our strength of evidence assessment we looked at dose-response association, strength of association, and reporting bias in nonrandomized studies. 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.[25] 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 reporting biases due to the questionable statistical validity of the available tests.

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 (e.g., the studies had medium risk of bias or the results were inconsistent or imprecise). We downgraded strength of evidence to low if two or more criteria were not met. We assigned a low level of evidence to nonrandomized studies but upgraded strength of evidence for strong or dose response associations. We defined evidence as insufficient if treatment effects or associations were examined by a single study with unclear or high risk of bias. We applied this approach regardless 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.[32]

Results

Of 5,244 identified references, we included 245 references of RCTs and 76 references of nonrandomized studies (detailed information about the results with references is available in the main body of the full report and in the evidence tables in Appendix D). 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 medium risk of bias. Proportions of low risk of bias RCTs varied among examined drugs. Most RCTs (86 percent) were double blind. We concluded unclear adequacy of allocation concealment in 94 percent of RCTs and unclear adequacy of

randomization in 51 percent of RCTs. Planned intention to treat was reported in 24 percent of RCTs.

The results were applicable to the target population. Most RCTs were conducted in the United States and Western countries, used the International Headache Society's definition, and enrolled mostly middle age women with episodic migraine suffering from an average of five monthly migraine attacks. RCTs enrolled on average 210 adults, measured the outcomes at 2 to 3 months of followup, and reported about 14 percent loss of followup (attrition rate).

Studies enrolled mostly adults (average age was 38 years) and adolescents. Few trials reported a proportion of obese subjects, but many participants were overweight according to the average body mass index. Most trials included patients with and without aura. Almost half of the enrolled subjects were naïve to migraine preventive drugs. Patient age and baseline migraine characteristics were similar in most trials. 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.

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

The 245 eligible references presented the results from RCTs. RCTs examined four approved drugs for episodic migraine (topiramate, divalproex, propranolol, and timolol), one approved drug for chronic migraine (onabotulinumtoxin A), and various off-label preventive drugs. Most trials examined a monotherapy with one active agent compared with placebo or another drug. 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 medium or high risk of bias and imprecise estimates from individual or meta-analyzed RCTs (Tables A–B). This executive summary focuses on pooled analyses from RCTs and the results from network meta-analysis. All results can be found in the main body of the full report.

KQ1a. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with placebo or no active treatment?

Prevention of Chronic Migraine

Only one drug for chronic migraine, Onabotulinumtoxin A, was examined in more than one RCT. Onabotulinumtoxin A was better than placebo in reducing monthly migraine attack by ≥50 percent in patients with baseline ≥15 migraine days per month (Table A). Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of onabotulinumtoxin A.

A single RCT reported that topiramate was better than placebo in achieving: (1) reduction of monthly migraine days from baseline; (2) 25 percent reduction in monthly migraine attacks, and (3) frequency of associated symptoms. Topiramate was not, however, better than placebo in

reducing monthly migraine attacks by ≥50 percent. The other individual RCT reported that propranolol added to topiramate did not effectively prevent chronic migraine in patients for whom topiramate monotherapy had failed.

Prevention of Episodic Migraine

All approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent in patients with baseline <15 migraine days per month (clinical response) (Table A). Drugs would achieve a clinical response preventing half or more migraine attacks in 200 to 400 patients per 1,000 treated. Clinicians need to treat three to five patients with episodic migraine to prevent half or more migraine attacks in one patient. Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of topiramate (from 50 to 100 mg/day with no additional benefits with 200 mg/day).

In addition to ≥50 percent reduction in monthly migraine frequency, individual RCTs of approved antiepileptic drugs and beta blockers improved other patient-centered outcomes. Topiramate demonstrated significant improvements for 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 reducing migraine attacks with nausea, vomiting, phonophobia, or photophobia. Topiramate and propranolol decreased use of drugs for acute migraine attacks.

Among ***off-label drugs,*** pooled analyses demonstrated that antiepileptic gabapentin, beta-blockers metoprolol, and calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by ≥50 percent (Table A).

Table A. Efficacy of migraine preventive pharmacological treatments, evidence from meta-analyzed randomized controlled clinical trials that compared active drugs with placebo

Active Preventive Treatment	Outcome	Sample	Rate, Percent With Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence (Reasons for Lowering SOE)
Onabotulinumtoxin A for chronic migraine	**≥50% decrease in migraine frequency**	**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 (medium ROB, imprecision)**
Topiramate 50 to 200mg/day for episodic migraine	100% decrease in migraine frequency	1,299	5.1 [2.6]	1.9 (1.0 to 3.4)	0.02 (-0.01 to 0.05)	NS	NS	Low (medium ROB, inconsistency, imprecision)
Topiramate for episodic migraine	≥75% reduction in monthly migraine days	1,086	22.3 [11.0]	1.9 (1.1 to 3.1)	0.10 (-0.01 to 0.20)	NS	NS	**Moderate** (imprecision)
Topiramate 50 to 200mg for episodic migraine	**≥50% reduction in monthly migraine days**	**1,145**	**42.2 [23.3]**	**1.7 (1.0 to 2.9)**	**0.18 (0.08 to 0.28)**	**6 (4 to 13)**	**179 (75 to 284)**	**Moderate (imprecision)**
Topiramate 50 to 200mg/day for episodic migraine	**≥50% reduction in monthly migraine frequency**	**1,422**	**49.6 [25.1]**	**2.0 (1.5 to 2.7)**	**0.29 (0.18 to 0.40)**	**3 (3 to 6)**	**288 (176 to 400)**	**Moderate (medium ROB)**
Divalproex for episodic migraine	**≥50% decrease in migraine frequency**	**405**	**43.0 [23.3]**	**2.2 (1.1 to 4.2)**	**0.24 (0.10 to 0.38)**	**4 (3 to 10)**	**241 (97 to 384)**	**Low (medium ROB, imprecision)**
Propranolol for episodic migraine	**≥50% decrease in migraine frequency**	**541**	**45.1 [22.3]**	**2.0 (1.5 to 2.7)**	**0.22 (0.14 to 0.30)**	**4 (3 to 7)**	**223 (142 to 304)**	**Low (medium ROB, imprecision)**
Timolol for episodic migraine	**≥50% decrease in migraine frequency**	**276**	**49.4 [23.3]**	**2.1 (1.5 to 3.1)**	**0.27 (0.15 to 0.38)**	**4 (3 to 6)**	**265 (154 to 377)**	**Low (medium ROB, imprecision)**
Gabapentin for episodic migraine	**≥50% decrease in migraine frequency**	**270**	**45. 9 [31.0]**	**1.5 (1.1 to 2.0)**	**0.17 (0.06 to 0.27)**	**6 (4 to 16)**	**165 (61 to 269)**	**Low (medium ROB, imprecision)**

Table A. Efficacy of migraine preventive pharmacological treatments, evidence from meta-analyzed randomized controlled clinical trials that compared active drugs with placebo (continued)

Active Preventive Treatment	Outcome	Sample	Rate, Percent With Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence (Reasons for Lowering SOE)
Metoprolol for episodic migraine	**≥50% decrease in migraine frequency**	**225**	**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)**	**Low (medium ROB, imprecision)**
Nimodipine for episodic migraine	**≥50% decrease in migraine frequency**	**126**	**28.6 [6.3]**	**4.5 (0.5 to 40.1)**	**0.23 (0.06 to 0.39)**	**4 (3 to 16)**	**229 (64 to 394)**	**Low (medium ROB, imprecision)**
Magnesium for episodic migraine	**≥50% decrease in migraine frequency**	137	33.8 [25.8]	1.3 (0.7 to 2.3)	0.08 (-0.09 to 0.26)	NS	NS	Low (inconsistency, imprecision)

CI = confidence interval; NS = Not significant; ROB = risk of bias; SOE = strength of evidence
Bold = significant effects of drugs on treatment response when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences.

Individual RCTs demonstrated that in patients with episodic migraine suffering from an average of five migraine attacks per month the off-label anti-epileptics carbamazepin and valproate (but not acetazolamide, lamotrigine, or oxcarbazepine) were better than placebo in reducing monthly migraine attacks by ≥50 percent. Individual RCTs demonstrated that off-label beta blockers acebutolol atenolol and nadolol (but not pindolol or alprenolol) were better than placebo in reducing monthly migraine attacks by ≥50 percent.

Individual RCTs of angiotensin inhibiting drugs demonstrated promising results. The angiotensin converting enzyme inhibitor captopril was examined in a single RCT. When tested in adults with comorbid hypertension and depressive symptoms for whom previous antimigraine drugs had been ineffective, the ACE inhibitor captopril was better than placebo in achieving complete cessation of migraine and improvement in headache index by ≥50 percent and in reducing depression symptoms. The ACE inhibitor lisinopril was better than placebo in reducing migraine days and migraine severity in patients with episodic migraine with or without hypertension. It reduced pain measured with SF-36, but did not decrease use of drugs for acute migraine attacks.

The 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 it had no effect on use of drugs for acute migraine attacks. In contrast, angiotensin II antagonist telmisartan was not better than placebo in reducing monthly migraine attacks by ≥50 percent.

KQ1b. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active pharmacologic treatments?

Pooled analysis was possible only for four paired drug comparisons (Table B). Most low-strength direct comparative effectiveness evidence came from individual head-to-head RCTs that demonstrated few significant differences between individual drugs.

Comparative Effectiveness of Onabotulinumtoxin A on Prevention of Chronic Migraine

Five individual RCTs provided low-strength evidence about the comparative effectiveness of onabotulinumtoxin A versus other drugs for chronic migraine prevention in 350 adults ages 18 to 65 with 12 to 24 monthly migraine days. Individual RCTs examined the comparative effectiveness of onabotulinumtoxin A 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 onabotulinumtoxin A; however, need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of onabotulinumtoxin A versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life.

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

Active Preventive Treatment	Outcome	Sample	Rate, Percent With Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence (Reasons for Lowering SOE)
Timolol vs. propranolol	≥50% decrease in migraine frequency	242	47.9 [52.1]	1.0 (0.7 to 1.2)	-0.03 (-0.15 to 0.10)	NS	NS	Low (medium ROB, imprecision)
Propranolol vs. metoprolol	≥50% decrease in migraine frequency	113	38.2 [50.0]	0.8 (0.5 to 1.2)	-0.12 (-0.30 to 0.06)	NS	NS	Low (medium ROB, imprecision)
Propranolol vs. Nifedipine	**≥50% decrease in migraine frequency**	**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)**
Metoprolol vs. Aspirin	≥50% decrease in migraine frequency	326	33.1 [39.3]	1.6 (0.2 to 11.0)	0.11 (-0.43 to 0.65)	NS	NS	Low (medium ROB, imprecision)

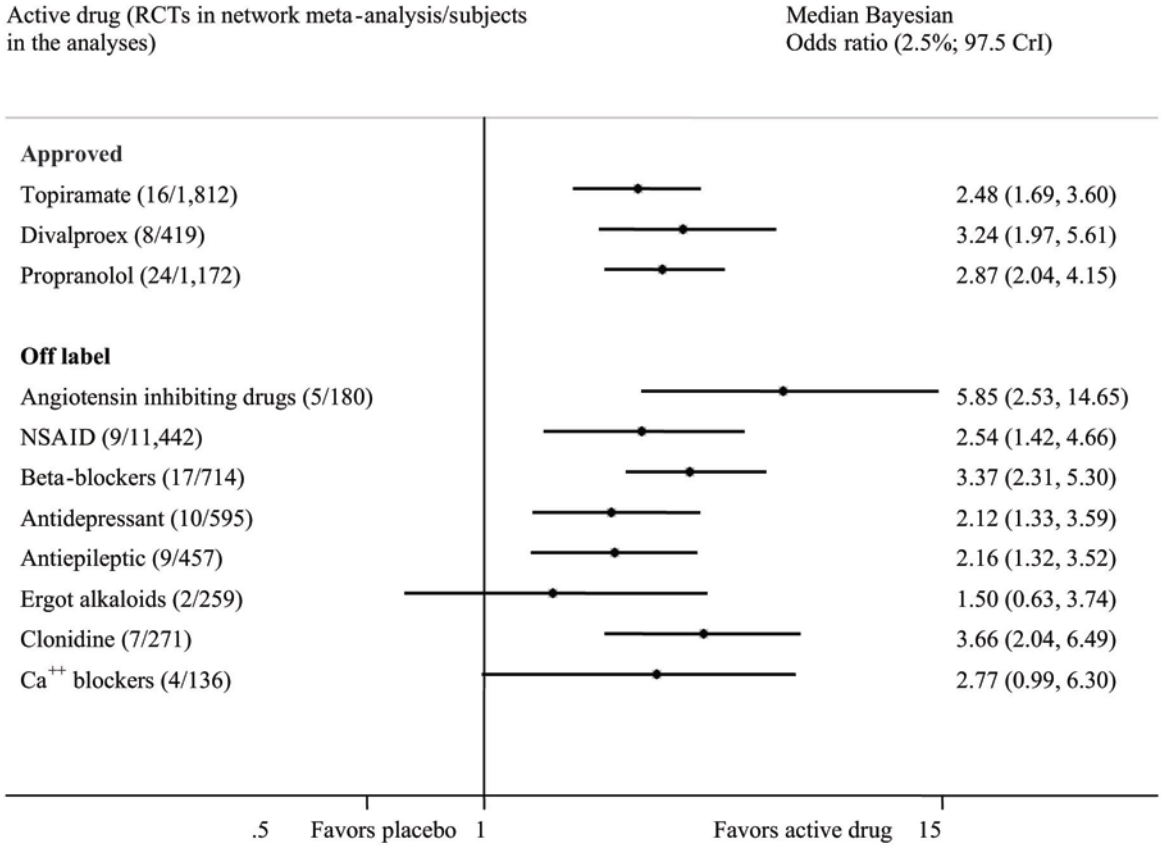
CI = confidence interval; NS = not significant; ROB = risk of bias; SOE = strength of evidence

Bold = significant effects of drugs on treatment response when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences. Line 3 is in bold.

Comparative Effectiveness of Approved Drugs on Prevention of Episodic Migraine

Pooled analyses demonstrated that decrease in headache frequency by≥50 percent did not differ with propranolol versus timolol or versus metoprolol (Table B). Propranolol was better than nifedipine in reducing monthly headache intensity by ≥50 percent. Indirect adjusted analysis demonstrated no differences among approved drugs in reducing monthly headache frequency by ≥50 percent. Exploratory network Bayesian meta-analyses demonstrated that approved drugs were similarly better than placebo. Among off-label drug classes, angiotensin inhibiting drugs demonstrated the largest significant odds of reducing monthly migraine by≥50 percent (Figure B).

Figure B. Bayesian network meta-analysis of clinical response to drugs versus placebo (66 RCTs of 14,774 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults



CrI = credible intervals; NSAID = nonsteroidal anti-inflammatory drugs
Clinical response was defined as ≥50% reduction in monthly migraine attacks or perceived clinically important treatment success. We used heterogeneous random effects model that assumes correlation within study (rho = 0.5) and heterogeneous between studies (WinBUG codes are in Appendix B).

KQ1c. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?

One RCT provided low-strength evidence that the likelihood of reducing monthly migraine frequency by ≥25 percent did not differ between propranolol and an intervention consisting of diaphragmatic breathing and systematic relaxation assisted by biofeedback and practiced at home. One RCT provided low-strength evidence that the likelihood of reducing monthly migraine frequency by ≥50 percent did not differ between exercising for 40 minutes three times a week, relaxation technique, or daily topiramate use.

KQ1d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic treatments alone?

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

KQe1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Individual RCTs provided low-strength evidence that increasing the dose of onabotulinumtoxin A, 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.

KQe2. 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 individual RCTs examined effectiveness of drug management for migraine prevention in 3,825 adults. Four RCTs examined the effectiveness of a multidisciplinary migraine management program compared with usual care. The trials offered low-strength evidence that 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.

Two RCTs examined the effectiveness of pharmacist-led drug management. The studies provided low-strength evidence that pharmaceutical care improved self-efficacy; an intensive pharmaceutical care campaign had no statistically significant impact on use of acute drugs.

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

We identified 15 RCTs and six nonrandomized studies that examined the safety of onabotulinumtoxin A for chronic migraine prevention in adults. We identified 159 RCTs of 18,134 adults that examined the safety of drugs for episodic migraine prevention in adults. We concluded that the results of these trials, which were a subset of RCTs that examined benefits

with drugs for episodic migraine prevention in adults, are applicable to the target population. The trials enrolled an average of 78 percent women. Mean age of the enrollees varied from 29 to 49 years. Patients had an average 5.5 monthly migraine attacks. On average, followup time for assessing adverse effects was 18 weeks. The sample size averaged 116 adults (range 12 to 818).

RCTs reporting harms were not necessarily powered to detect statistically significant differences in adverse effects. We concluded medium risk of bias in 104 RCTs and low risk of bias in 36 RCTs. Most studies (133 RCTs) were double blind. We focused on treatment discontinuation due to any and specific adverse effects from pooled analyses.

KQ2a. What are the harms from preventive pharmacologic treatments when compared with placebo or no active treatment?

Adverse Effects With Drugs for Chronic Migraine

Onabotulinumtoxin A resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo (Table C). Increase in risk of adverse effects was dose responsive. Increasing doses of onabotulinumtoxin A to 150 to 225U resulted in greater risk of blepharoptosis, muscle weakness, and neck rigidity. Among specific adverse effects, onabotulinumtoxin A increased risk of back or neck pain, dysphagia, hypertonia, blepharoptosis, and muscle weakness.

Adverse Effects With Drugs for Episodic Migraine

Bothersome adverse effects leading to treatment discontinuation were examined in 68 RCTs.

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 C). Published pooled analysis of individual patient data demonstrated discontinuation of topiramate treatment due to anorexia, anxiety, depression, and hypesthesia. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk of dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.

In comparisons of divalproex or valproate versus placebo, treatment discontinuation due to any adverse effects did not differ. However, individual RCTs reported that divalproex caused nausea, somnolence, tremor, vomiting, and asthenia, leading to treatment discontinuation.

Propranolol caused bothersome adverse effects leading to treatment discontinuation more often than placebo (Table C). Among specific adverse effects, propranolol increased risk of diarrhea and nausea. Timolol increased risk of any adverse effects but not bothersome harms that led to treatment discontinuation.

Among off-label drugs, pooled analyses demonstrated that the off-label antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo (Table C).

Table C. Treatment discontinuation due to adverse effects with migraine preventive drugs in adults, evidence from meta-analyzed randomized controlled clinical trials

Active Preventive Treatment	Sample	Rate, Percent With Active Drug [Control]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence (Reasons for Lowering SOE)
Compared With Placebo							
Onabotulinumtoxin A	**1,384**	**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 (medium ROB)**
Topiramate	**2,055**	**16.6 [8.5]**	**1.8 (1.3 to 2.4)**	**0.06 (0.02 to 0.11)**	**16 (9 to 53)**	**63 (19 to 107)**	**Low (medium ROB, Imprecise)**
Divalproex	346	9.8 [7.8]	1.2 (0.5 to 2.7)	0.02 (-0.05 to 0.10)	NS	NS	Low (medium ROB, imprecise, inconsistent)
Valproate	150	6.7 [5.3]	1.3 (0.3 to 4.9)	0.01 (-0.07 to 0.08)	NS	NS	Low (medium ROB, imprecise)
Propranolol	**221**	**13.2 [5.6]**	**2.1 (0.6 to 7.7)**	**0.06 (0.00 to 0.12)**	**16 (8 to 333)**	**62 (3 to 120)**	**Low (medium ROB, imprecise, inconsistent)**
Gabapentin	270	17.0 [7.7]	1.9 (0.9 to 4.2)	0.07 (-0.01 to 0.15)	NS	NS	Low (medium ROB, imprecise)
Lamotrigine	178	12.8 [6.0]	2.4 (0.5 to 12.2)	0.14 (-0.17 to 0.44)	NS	NS	Low (imprecise, inconsistent)
Amitriptyline	**507**	**11.2 [5.8]**	**1.9 (1.0 to 3.5)**	**0.05 (0.01 to 0.10)**	**19 (10 to 167)**	**54 (6 to 102)**	**Low (medium ROB, imprecise)**
Femoxetine	124	11.7 [6.3]	1.9 (0.6 to 6.1)	0.05 (-0.05 to 0.15)	NS	NS	Low (medium ROB, imprecise)
Clonidine	334	2.4 [0.6]	2.8 (0.4 to 18.5)	0.02 (-0.01 to 0.05)	NS	NS	Low (medium ROB, imprecise)
Nimodipine	155	3.9 [6.3]	0.7 (0.2 to 2.6)	-0.03 (-0.09 to 0.04)	NS	NS	Low (medium ROB, imprecise, inconsistent)
Naproxen	172	3.5 [1.2]	2.3 (0.3 to 15.4)	0.02 (-0.03 to 0.07)	NS	NS	Low (high ROB, imprecise, inconsistent)
Magnesium	150	7.7 [1.4]	3.8 (0.7 to 22.4)	0.06 (0.00 to 0.13)	NS	NS	Low (inconsistent, imprecise)
Compared With Active Treatment							
Topiramate vs. mitriptyline	399	18.3 [21.3]	0.9 (0.6 to 1.3)	-0.04 (-0.11 to 0.04)	NS	NS	Low (medium ROB, imprecision)

CI = confidence interval; NS= not significant; ROB = risk of bias; SOE = strength of evidence

Bold = significant effects of drugs on treatment response and discontinuation due to adverse effects when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences. Lines 1, 2, 5, and 8 are in bold.

KQ2b. What are the harms from preventive pharmacologic treatments when compared with active pharmacologic treatments?

Comparative Harms With Drugs for Prevention of Chronic Migraine

Individual RCTs demonstrated less frequent treatment discontinuation due to adverse effects with onabotulinumtoxin A than topiramate or amitriptyline. Onabotulinumtoxin A versus divalproex sodium resulted in a higher risk of ptosis.

Comparative Harms With Drugs for Prevention of Episodic Migraine

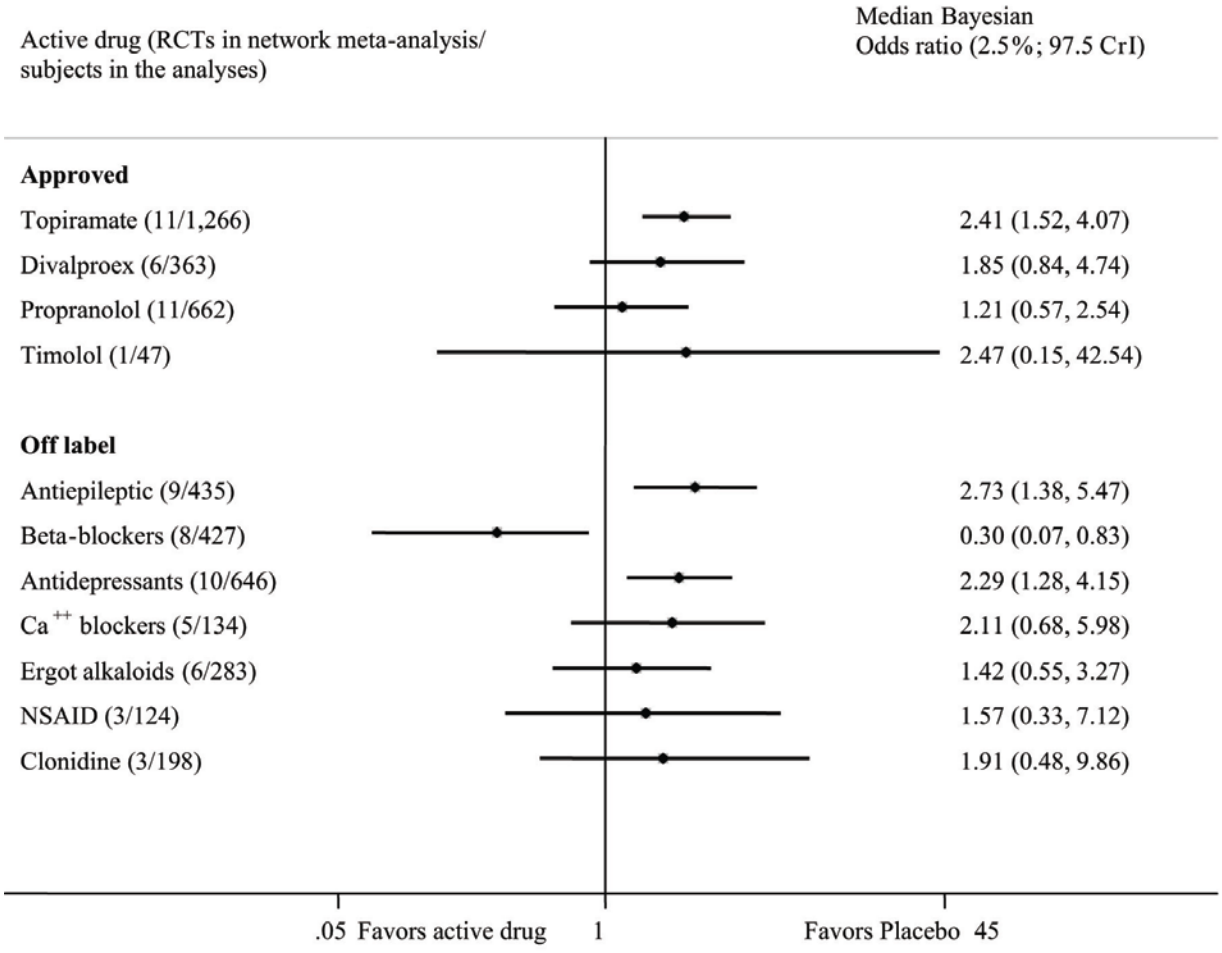
Pooled analysis showed no differences in treatment discontinuation with topiramate versus amitriptyline (Table C). Individual unique RCTs provided low-strength direct evidence about adverse effects with specific drugs. We observed no consistent pattern across available drug comparisons.

Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analyses demonstrated that topiramate and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Figure C). According to network meta-analysis, off-label angiotensin inhibiting drugs and beta-blockers were the safest treatment option for adults with episodic migraine.

KQ2c. 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.

Figure C. Bayesian network meta-analysis of treatment discontinuation due to intolerable adverse effects with drugs versus placebo (47 RCTs of 3,054 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults



CrI = credible intervals; NSAID = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial

KQ 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

Onabotulinumtoxin A 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. Onabotulinumtoxin A decreased the likelihood of acute drug use in patients with a baseline of more than 12 monthly migraine days (RR 0.78, 95% CI, 0.66 to 0.92).

Amitriptyline was better than placebo in reducing monthly migraine, but only in patients with depression or 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% CI, 1.45 to 3.8 for every additional day of migraine at baseline).

Concurrent Prophylactic Medication Use

Onabotulinumtoxin A more often than placebo led to adverse effects, blepharoptosis, muscle weakness, and neck pain, regardless 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 one low-risk-of-bias RCT. Per 1,000 women treated, topiramate would cause a complete cessation of migraine attacks in 37 (95% CI, 8 to 67) and a reduction of monthly migraine attacks by ≥50 percent in 249 (95% CI, 178 to 320). However, both men and women experienced a reduction of monthly migraine 75 to 90 percent more often with topiramate than with placebo.

Prior Medication Use

One RCT that examined adding propranolol to topiramate for subjects who had chronic migraine and for whom previous topiramate monotherapy failed. The study separated subgroups by prior topiramate use or overuse of the drugs for acute migraine. Propranolol with topiramate was not better than topiramate alone in reducing migraine frequency, regardless of the prior drug history of the patients. Changes in quality of life score (from baseline) varied depending on prior topiramate use. Patients with prior stable topiramate use experienced worsening in quality of life with combined therapy versus improvement in quality of life with topiramate monotherapy. In contrast, patients without stable prior topiramate use experienced improvement in quality of life with combined therapy versus statistically insignificant changes with topiramate monotherapy.

Presence of Aura

No trials directly compared drug effects in patients with and without aura. Several post hoc subgroup analyses of topiramate versus placebo provided inconsistent evidence of the drug efficacy in respect to aura. Two publications suggested that topiramate was better than placebo in patients with aura. Post hoc subgroup analysis of one RCT found statistically significant reduction in migraine frequency with topiramate versus placebo (-2.43 vs. -0.79 respectively, p value = 0.02) only in subjects with aura. Post hoc subgroup analysis of the other RCT found that in patients with aura, topiramate was better than placebo reducing migraine frequency, number of migraine days, severity and duration of attacks, and photophobia. In contrast, post hoc analysis of the Prolonged Migraine Prevention (PROMPT) found that topiramate efficacy was similar in patients with and without aura.

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

Discussion

All approved drugs, some off-label beta blockers, and the angiotensin inhibiting drugs were better than placebo in reducing monthly migraine frequency by≥50 percent (clinical response). The relative effect size of drugs was moderate: drugs would result 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 medium risk of bias in more than half of included RCTs. Strength of evidence was moderate only for topiramate, 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. We found it difficult to evaluate the role of financial conflict of interest and industry sponsor participation in data analyses and interpretation because many studies were conducted prior to mandatory requirements for financial disclosure, leading to inconsistent reporting and insufficient detail from individual studies.[33] 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 also inconsistently reported.

The results were applicable to the target population 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.[34] 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).[35,36] No trials examined the role of genetic polymorphism in drug metabolism and effects. Migraine prevention trials did not address teratogenic effects, anorgasmia, impotence, and other harms of anti-epileptic drugs that can deter long-term adherence to preventive drugs.

Few RCTs reported treatment effects in patient subgroups. Low strength of evidence suggested that onabotulinumtoxin A and amitriptyline were more effective in patients with frequent baseline migraine suffering from ≥15 monthly migraine days. Our review demonstrated that a relative risk of adverse effects with onabotulinumtoxin A was lower in trials with higher placebo rates of adverse effects. Previous research demonstrated that compared with patients with epilepsy, patients with migraine more often quit taking topiramate due to bothersome adverse effects.[15] 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 inhibiting drugs and beta blockers were the most effective and tolerable drugs. Head-to-head trials were not designed to test safety with migraine preventive drugs. Network meta-analysis demonstrated that

patients stopped taking active drugs more often than placebo with topiramate, off-label antiepileptics, antidepressants, and ergot alkaloids. 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.[37] The most recent guidelines from the American Academy of Neurology and the American Headache Society recommend the four FDA-approved drugs—the antiepileptics topiramate and divalproex and the beta-blockers propranolol and timolol—for adult migraine prevention.[38]

The aforementioned guidelines, which focused on published evidence, differed in regard to recommending off-label drugs. Further, current guidelines do not include consideration of the balance between benefits and harms of drugs as a basis for clinical decisonmaking.[39] Our review analyzed benefits and harms of drugs and provided evidence for using effective and relatively safe off-label angiotensin inhibiting drugs and off-label beta-blockers as alternatives based on patient preferences, comorbidities, and contraindications to the medications.

The most effective and safest drugs should be the first choice in adult migraine prevention. We found no published controlled observational studies about preventive drug use or about comparative effectiveness of approved versus off-label drugs. We found no studies that examined use of medical treatment for adverse effects with drugs.

Some evidence suggests that off-label drug use is common in the United States, with little or no scientific support.[40] 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 uses, with the most common being anticonvulsants, gabapentin, and amitriptyline hydrochloride.[41] We found that off-label antiepileptics and antidepressants demonstrated worse benefits and safety profiles than beta blockers or angiotensin inhibiting drugs. Evidence of off-label drug use and associated adverse effects has been evaluated with prospective pharmacovigilance surveys in European countries.[42,43] Routine monitoring of harms with off-label drugs via collecting and analyzing evidence of comparative safety in clinical settings is needed in the United States.

Our review found poor results availability from all conducted studies and possible reporting bias in outcomes reporting from completed and published 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 results on the Clinicaltrials.gov Web site reported all harms regardless of rates or assumed causal association with active drugs.

Our report has limitations. 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 consistent 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 pharmacologic 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.

Future Research Needs

We identified gaps and biases in available evidence that should direct future research. Well-designed randomized 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 potential treatment-modifying effects of patient age, sex, race, migraine family history, comorbidities, and prior treatment with migraine preventive drugs. Observational studies should analyze off-label drug use 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. The long-term preventive benefits of and adherence to 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 treatment modifying effects of patient characteristics on long-term drug benefits and safety.

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 (onabotulinumtoxin A, topiramate, divalproex, timolol, and propranolol) and off-label beta blockers were better than placebo in reducing monthly migraine frequency by ≥50 percent. However, topiramate and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.

Key Messages

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

Effect of Preventive Pharmacologic Treatments on Patient-Centered and Intermediate Outcomes Compared With Placebo or no Active Treatment

- For chronic migraine, onabotulinumtoxin A was more effective than placebo in reducing monthly chronic migraine attacks by ≥50 percent with inconsistent improvement in quality of life.
- For episodic migraine, all approved drugs (topiramate, divalproex, propranolol, and timolol) were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response).
- Relative effect of drugs was moderate: drugs would result in clinical response in 200 to 400 patients per 1,000 treated.
- Strength of evidence was low due to medium risk of bias and imprecise estimates.
- Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of onabotulinumtoxin A and topiramate (from 50 to100 mg with no additional benefits with 200 mg/day).
- Among off-label drugs, pooled analyses offered low-strength evidence that the antiepileptic gabapentin, beta-blocker metoprolol, and the calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by ≥50 percent.
- Individual RCTs offered low-strength evidence that the off-label beta blockers acebutolol atenolol and nadolol were better than placebo in reducing monthly migraine attacks by ≥50 percent. Individual RCTs demonstrated that angiotensin converting enzyme inhibitors captopril and lisinopril and angiotensin II antagonist candesartan were better than placebo in reducing monthly migraine attacks by ≥50 percent.

Effect of Preventive Pharmacological Treatments on Patient-Centered and Intermediate Outcomes Compared With Active Pharmacological Treatments

- Individual RCTs provided low-strength direct evidence about the comparative effectiveness of drugs and demonstrated few significant differences between drugs.
- Indirect adjusted analysis demonstrated no differences between approved drugs and greater odds of a clinical response with the angiotensin II antagonist candesartan.
- Exploratory network Bayesian meta-analyses demonstrated that approved drugs were similarly better than placebo. Among off-label drug classes, angiotensin inhibiting drugs demonstrated the largest significant odds of reducing monthly migraine by ≥50 percent.

Effect of Preventive Pharmacologic Treatments on Patient-Centered and Intermediate Outcomes Compared With Active Nonpharmacologic Treatments

- Individual RCTs provided low-strength evidence of no difference between propranolol and biofeedback for achieving a ≥50 percent reduction in monthly migraine attacks.

Influence of Approaches to Drug Management Versus Usual Care (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.
- A headache management program resulted in complete cessation of migraine (100 percent reduction in monthly migraine attacks).
- 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

- Among approved drugs, onabotulinumtoxin A, topiramate, and propranolol resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- The association was dose responsive for topiramate. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk of dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.
- Individual RCTs showed that divalproex led to treatment discontinuation due to adverse effects that included nausea, somnolence, tremor, vomiting, and asthenia.
- Among other drugs, pooled analyses demonstrated that off-label antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo.
- Limited low-strength evidence from individual head-to-head RCTs suggested that treatment discontinuation due to adverse effects was less frequent with onabotulinumtoxin A than topiramate or amitriptyline.
- Individual unique RCTs provided low-strength direct evidence about adverse effects with specific drugs, with no consistent pattern across available drug comparisons.
- Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analyses demonstrated that topiramate, off-label antiepileptics, and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. According to network meta-analysis, off-label angiotensin inhibiting drugs and beta-blockers were the safest treatment option for adults with episodic migraine.

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.
- Onabotulinumtoxin A was more effective in patients with a higher mean baseline migraine frequency.
- Amitriptyline was better than placebo in reducing monthly migraine, but only in patients with frequent migraine attacks and in depressed patients with baseline severe migraine.

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

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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 can 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, the American Migraine Prevalence and Prevention expert advisory group recommends that prevention for episodic migraine defined as ≥4 monthly migraine days with normal functioning or ≥2 migraine days with severe impairment.[9] For 1.4 to 2.2 percent of those who experience migraine, the condition is chronic[10] as defined by the National Headache Foundation (i.e., headache that occurs >15 days per month for at least 3 months).[11,12] Both migraine types significantly affect 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 adults with episodic migraine and all adults with chronic migraine 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, onabotulinumtoxin A. Doctors also prescribe off-label drugs (approved for clinical conditions other than migraine prevention) for migraine prevention, including novel antiepileptic drugs, calcium channel blockers, serotonin and noradrenaline reuptake inhibitors, glutamate blockers, and drugs from several other classes.[20,21]

Preventive treatment aims to eliminate headache pain without intolerable harms.[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 relieving pain, preventive drugs can decrease severity of migraine attacks, reduce 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.[11,22,23,29,30] 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.[11,12,31] 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 pharmacologic and nonpharmacologic treatment options.[32] 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.[32,33] The majority of patients seen in headache specialty clinics that practice multidisciplinary coordinated care had chronic migraine.[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, this review focuses on outpatient care.

Topic Refinement and Review Protocol

The topic was anonymously nominated via the public domain. During the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of neurology, primary care, consumers, scientific experts, and payers, to help define the Key Questions (KQs).[34] The KQs were then posted for public comment for 4 weeks, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol, which was then refined based on their input, reviewed by AHRQ, and posted for public access from April 12, 2012, to May 10, 2012, at the AHRQ Effective Health Care Web site.

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[35,36] and PRISMA guidelines.[37] The protocol is posted in the systematic review registry (protocol registration number is CRD42012001918, available at www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42012001918).[38]

Key Questions

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

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

c. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?
d. How do preventive pharmacologic treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic 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?

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

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

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

Methods

We followed an a priori research protocol that we developed with the clinical and methodological input of a technical expert panel. The protocol followed the Effective Health Care Program's "Methods Guide for Effectiveness and Comparative Effectiveness Review."

Literature Search Strategy

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 May 20, 2012. We searched the FDA Web site for medical and statistical reviews of 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.

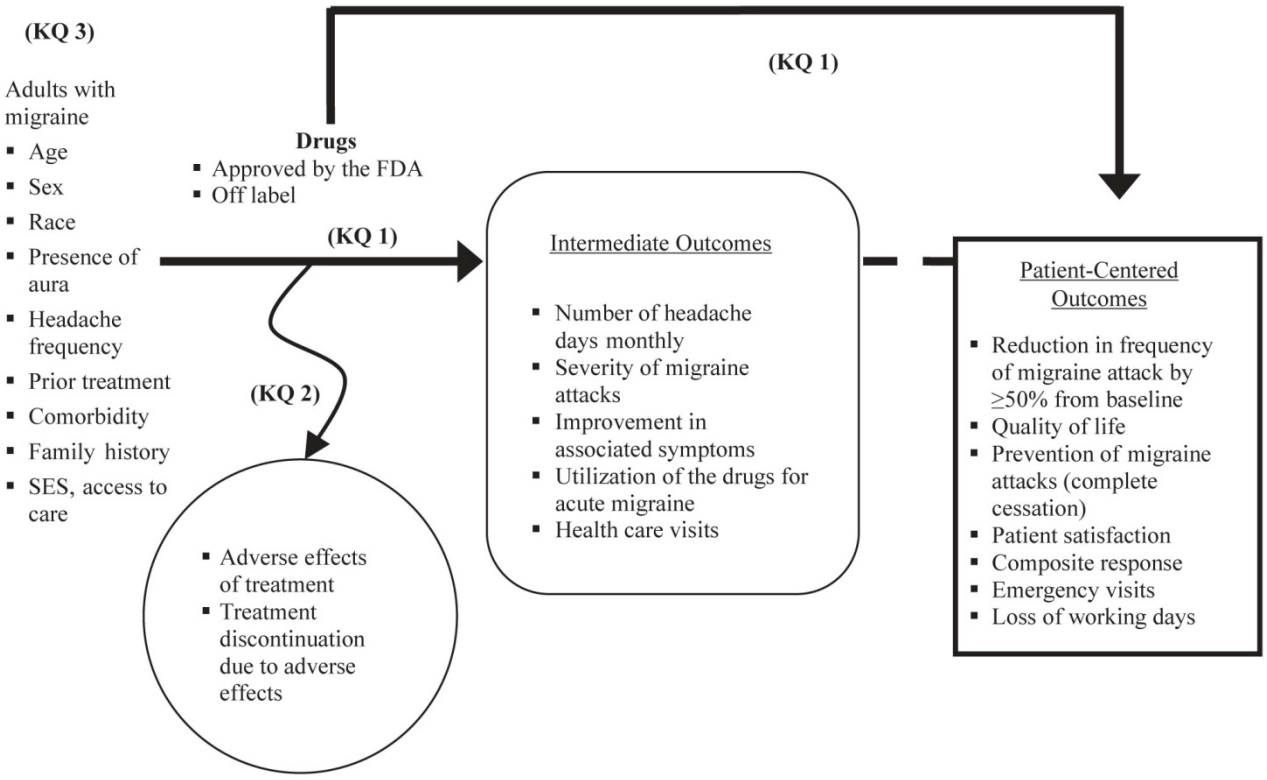
Searches for relevant literature involved several steps: (1) evaluating previously published systematic reviews,[39] (2) conducting a comprehensive literature search in the databases listed above to retrieve identified references, (3) screening abstracts against the inclusion/exclusion criteria, and (4) reviewing full text articles of eligible studies to determine potential inclusion in the synthesis.

Inclusion Criteria

- Original epidemiologic studies that aimed to examine preventive pharmacologic treatments for migraine.
- Publication in English.
- 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 (Appendix B).[11]
- Eligible intermediate and patient-centered outcomes as listed in Figure 1.
- Drugs approved by the FDA for migraine prevention and off-label drugs examined in clinical trials (Appendix B Table 1).

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

Figure 1. Analytical framework[35,36,40]



KQ = Key Question; SES = socioeconomic status
K1 What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in adults?
K2 What are the comparative harms from pharmacologic treatments for preventing migraine attacks in adults?
K3 Which patient characteristics predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks in adults?

Exclusion Criteria

- Studies of treatments aimed at acute migraine attacks.
- 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.[41,42,43] Studies of short-term prevention of migraine, including menstrual migraines.
- Studies that included some patients with migraine but did not separately report 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 examined eligible drugs on populations with other diseases.

Study Selection

We followed the AHRQ Methods Guide to select evidence from controlled trials and observational studies.[44] Three investigators worked independently to determine study eligibility resolving disagreements through discussion.[45] 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.[44] To assess harms of treatments, we included published and unpublished evidence of the adverse effects of drugs in patients with migraine.[46] We defined harms as a totality of all possible adverse consequences of an intervention[46] 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 (Population, Intervention, Comparator, Outcomes, Timing, and Settings). We defined the target population as community-dwelling adults with episodic or chronic migraine. We formulated a list of eligible interventions after discussions with key informants and technical experts and after consideration of public comments (Appendix B Table 1). Eligible comparators included pharmacologic, nonpharmacologic, and combined preventive treatments. We defined eligible intermediate and patient-centered outcomes (presented in the analytical framework in Figure 1).

Data Extraction

Researchers used standardized forms to extract data (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy). 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. We abstracted means and standard deviations of continuous variables to calculate mean differences with a 95% confidence interval (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 assuming that the same proportions apply in the missing data. [45] 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, baseline frequency, severity, and prior treatment status) as factors that can modify treatment effects. We abstracted the definition of migraine used in each study. 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.

Risk of Bias Assessment

We evaluated the risk of bias in individual studies of benefits and harms according to recommendations from the "Cochrane Handbook for Systematic Reviews of Interventions."[45] First, we classified studies by their design as either interventional (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 risk of bias tool in interventional studies,[47] we evaluated: (1) random allocation of the subjects to the treatment groups; (2) masking of the treatment status to the participants and investigators; (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 with methods section in the articles. Since all outcomes in the review were self-reported, masking of outcome assessment was not essential in evaluating risk of bias, but masking of treatment was. Masking of treatment status was not feasible for RCTs that examined nondrug therapies as comparators; therefore, we did not include it in risk-of-bias assessment for those studies.

We assumed a low risk of bias when RCTs met all the risk of bias criteria, a medium 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.[48] 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 adjustment for confounding factors to address selection bias and exclusion of subjects from the analyses to address attrition biases.[49]

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.

Data Synthesis

We categorized drugs according to The Anatomical Therapeutic Chemical Classification System of the World Health Organization. Accordingly, we categorized botulinum toxin treatments under one category-M03AX01. We analyzed together and separately the effects of onabotulinumtoxin A (approved by the FDA), botulinum neurotoxin type A, and abobotulinumtoxin A.

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.[50,51] Synthesis of evidence about comparative benefits and safety with drugs from individual RCTs was restricted to studies with low or medium 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 most recent migraine definition proposed by the International Headache Society.[11] Thus, older eligible studies published before 2004 defined migraine according to previous definitions of the International Headache Society or according

to definitions of the Ad Hoc Committee on Classification of Headache.[52] We compared baseline patient characteristics and treatment effects depending on the exact migraine definition and here we report the results when they differed significantly.

Using Meta-Analyst[53] and STATA®[54] software, we calculated the relative risk and absolute risk difference from the abstracted events. We evaluated statistical significance at a 95 percent confidence level. We used default software continuity coefficients for 0 events and intention to treat as recommended calculations for missing data. We hypothesized superiority of drugs versus placebo and versus each other.[55]

For continuous outcomes we calculated the mean differences from the reported means and standard deviations. We also calculated ratios of means that describe clinically interpretable percentage differences in outcomes with active versus control treatments.[56] We calculated Cohen standardized mean differences for different measures of the same outcome.

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 (0.5 as a default option in both software applications) and intention to treat as recommended calculations for missing data.[45]

For sparse adverse effects data, we used multiple models to test robustness of inferential statistics. Models included random and fixed effects inverse variance methods, maximum likelihood methods, Peto odds ratio,[57] double arcsine transformation for comparing two proportions, and odds ratios from random-effects generalized nonlinear mixed-effect models.[53,58-61]

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 and pooled Cohen standardized mean differences for different continuous measures of the same outcome. In cases of multiarm trials, we created a single pair-wise comparison.[47] To avoid the spurious increase in precision in multiarm trials, we divided placebo arms approximately evenly among the comparisons according to randomization ratio.[45,62]

We tested consistency in the results by comparing the direction and strength of the association.[63] We assessed heterogeneity in results with Chi-squared and I-squared tests.[64,65] We explored heterogeneity with meta-regression and sensitivity analysis; we report the results from random effects models only.[66] 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.[57] 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.[66]

We calculated the number needed to treat to achieve one event of a patient-centered outcome as reciprocal to absolute risk differences (ARD) in rates of outcome events in the active and control groups.[54,67] We calculated means and 95% CIs for the number needed to treat as reciprocal to pooled ARD when ARD was significant.[68] 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.

In cases when very few studies were available to provide evidence from direct head-to-head comparisons, we conducted indirect comparisons. To conduct indirect comparisons, we used

statistical techniques to estimate the treatment effects from studies of each given treatment against controls under an assumption of consistency.[69-73]

- We used adjusted indirect frequentist comparisons for individual drugs that were compared with placebo.[71] This analysis provided pair-wise triangular comparisons for drugs that were compared with placebo rather than network meta-analysis.
- To address the problems with inevitable differences across studies, we used mixed (or multiple) treatment comparisons (MTCs), or so-called network meta-analysis.[71-73] Network meta-analysis refers to methods that, in the absence of head-to-head comparisons, compare treatments by combining all available evidence from studies that form a network of evidence (including studies that compare three or more treatment arms).

By synthesizing direct and indirect comparisons, we improved the precision of estimates for treatment effects. A Bayesian analysis can easily construct complicated models with fewer assumptions. Bayesian analysis also permits explicit posterior inference regarding the probability that each treatment is "best" for a specific outcome.[74-76] We calculated Bayesian odds ratios[53,61] with 2.5 to 97.5 percent credible intervals. We conducted exploratory Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments (Appendix B Table 2).[77] We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class demonstrated no significant differences in outcomes. We compared odds ratios from network meta-analyses with odds ratios from direct head-to-head RCTs to examine consistency of the estimates.[78] We concluded no differences in drug effect (hereafter called similar effects) if confidence or credible intervals included one (no effect or no difference).[79] All Bayesian results were obtained from the WinBUGS software,[80] using Markov chain Monte Carlo (MCMC) samples after a 50,000-sample algorithm burn-in. WinBUG codes are presented in Appendix B Table 3.

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 including reduction in monthly migraine frequency by 100 percent or ≥50 percent, patient global assessment of treatment success, rates of clinically important improvement in migraine-related disability and quality of life. We also assessed treatment discontinuation due to harms.[63] We based our criteria on published guidelines acknowledging inevitable subjectivity of the assessment.[47,81] We assigned a medium or high risk of bias in the body of evidence when at least one individual RCT had medium or high risk of bias, respectively.

We defined treatment effect estimates as precise when pooled estimates had reasonably narrow 95% CIs, and pooled sample size was greater than 300 (using 25% relative effect difference for calculation of optimal information size).[82] 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 reporting biases due to the questionable statistical validity of the available tests.[83] We assess publication bias by analyses of the publication rates of the registered studies and the NIH funded studies. We assess selective reporting of the patient centered outcomes by comparing protocols with published results.

In assessing strength of evidence, we looked at dose-response association, strength of association, and reporting bias in nonrandomized studies. 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.[45] We defined low magnitude of the effect when relative risk is significant but <2.

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 medium 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 assigned a low level of evidence to nonrandomized studies and upgraded strength of evidence for strong or dose response associations. We defined evidence as insufficient when a single study with high risk of bias examined treatment effects or associations. We applied this approach regardless of whether the results were statistically significant.

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.[79] Studies of community-dwelling adults receiving drug treatments with 6 or more months of followup had high applicability, as did large observational cohorts based on national registries, population-based effectiveness trials, and nationally representative administrative and clinical databases.

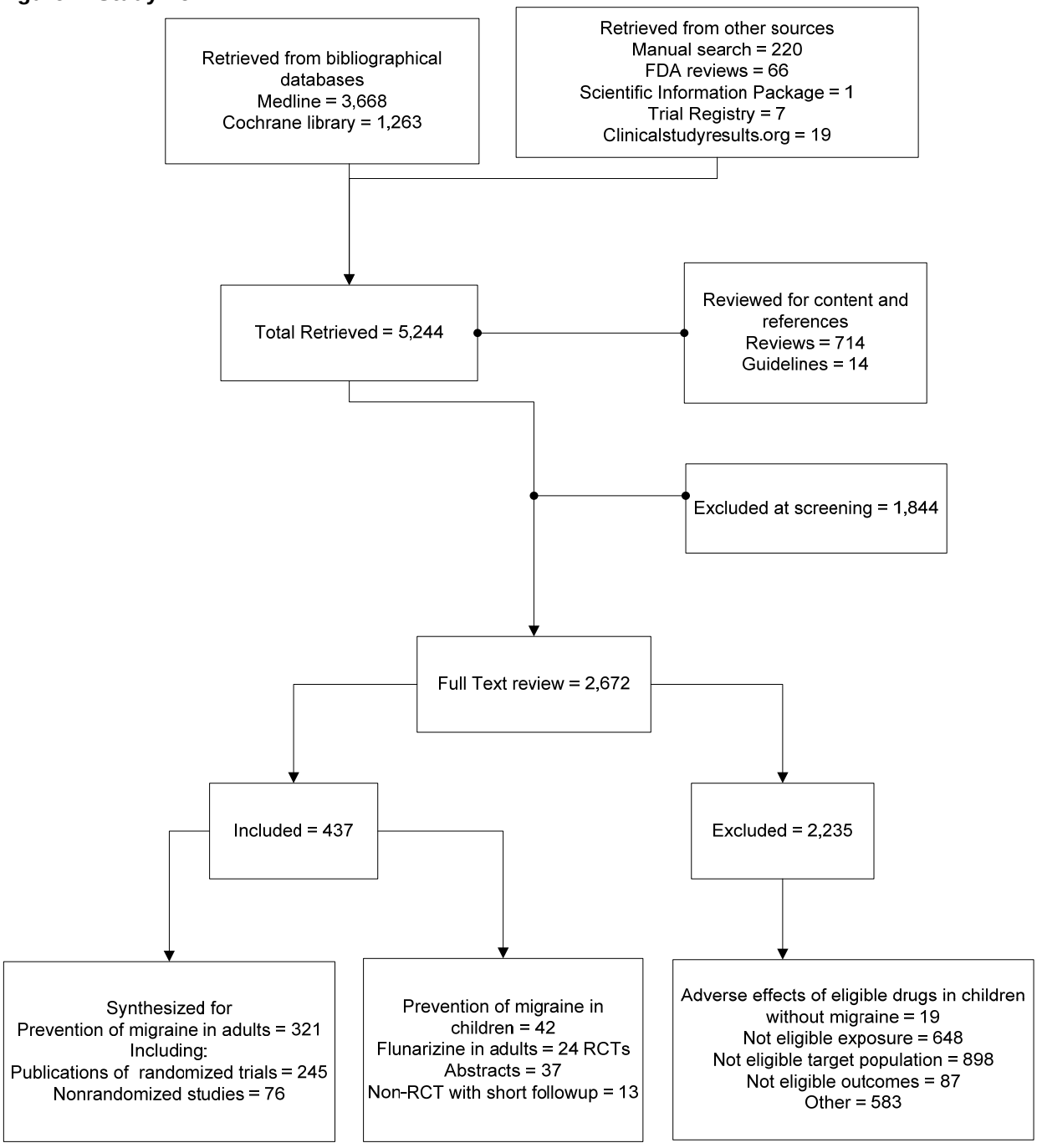
Peer Review and Public Commentary

We invited external peer review of this Comparative Effectiveness Review (CER) from experts in migraine management fields and individuals representing stakeholder and user communities; AHRQ and an associate editor also provided comments. The draft report was posted on the AHRQ Web site for 4 weeks to elicit public comment. We addressed all reviewer comments, revised the text as appropriate, and documented everything in a disposition of comments report that will be made available 3 months after the Agency posts the final CER on the AHRQ Web site.

Results

Of 5,244 identified references, we included 245 references of RCTs and 76 nonrandomized studies (Figure 2). All excluded references are presented in Appendix C.

Figure 2. Study flow



Publication Bias

By analyzing the NIH-funded and registered studies, we found that the results are available from only a small proportion of migraine prevention studies. However, we could not determine exact reasons for low availability of results based on available data. Both, posting of results and publication rates, varied by individual sponsors.

We found 18 NIH funded grants that aimed to examine migraine prevention. Six grant projects funded three RCTs. Two of those three RCTs were registered in ClinicalTrials.gov (Table 2). Overall publication rate was 44 percent (eight of 18 funded projects). The National Institute of Neurological Disorders and Stroke funded nine studies (the largest number among the agencies), and published the results from four of these projects (Table 2). We could not explain why the studies have not been published because the NIH grant database does not allow the analysis of the exact reasons for the low publication rates of the projects. Results from the NIH-funded projects were published after 1.9 to 3 years from the end dates of the projects (Table 3). Time intervals between project end dates and publication did not differ among the funding agencies.

Searching trial registries, we found 67 studies in ClinicalTrials.gov and 24 studies in other registries. Publication rates of study results were slightly lower for the studies registered in ClinicalTrials.gov (21 percent; 14/67) than in other registries (33 percent; 8/24). Among the studies registered in ClinicalTrials.gov most studies examined drugs (61/67). A placebo control was used by 64 percent (43/67). Most studies were completed (70 percent; 47/67) and four studies were terminated. Termination due to harms with treatments was clearly indicated in two terminated studies. The results were posted for nine studies (13 percent).

Publication rates varied depending on subjects and study characteristics (Table 4). Only 28 percent of all completed studies, 50 percent of biologics studies, and 18 percent of drug studies were published. Only 33 percent of Phase III and 50 percent of Phase IV studies were published. No terminated studies were published. Publications occurred an average of 2 years after study completion (0.5 to 6.6 years). Publication time varied among individual sponsors. Odds of publication did not reach statistical significance, probably due to the small number of studies (Table 5).

The rates of the posting of the results also varied depending on subjects and study characteristics (Table 4). Half of biologics studies and 12 percent of drug studies posted the result in ClinicalTrials.gov. Only 13 percent of Phase III and 29 percent of Phase IV trials posted the results in ClinicalTrials.gov. Trials that were terminated for safety reasons did not post the results. Results were posted an average of 2.6 years after study completion dates (0.9 to 5.2 years). Biologic studies posted the results an average of 3 years after completion dates, and drug studies posted results an average of 2.6 years after completion dates. Placebo-controlled studies posted results an average of 2.5 years after completion dates, and comparative effectiveness studies 3.4 years after completion dates. Terminated studies posted the results an average of 5 years after study termination. Odds of posting the results did not reach statistical significance, probably due to the small number of studies (Table 5).

Table 2. Registration, publication, and cost of the NIH-funded grants aimed at migraine prevention (as of May 2012)

Agency	Not Registered	Registered	Total	% Registered	Unpublished	Published	Total	% Published	Sum/Cost of Studies With No Results Available	Minimum Cost	Maximum Cost
NCCAM	1	2	3	67	1	2	3	67	$675,532/ $222,925	$100,000	$292,000
NCI	2	0	2	0	2	0	2	0	$176,000/ $176,000	$88,000	$88,000
NIDA	2	0	2	0	0	2	2	100	$791,080	$283,941	$507,139
NIMH	1	0	1	0	1	0	1	0	Not reported		
NINDS	7	2	9	22	5	4	9	44	$1,159,146/ $649,121	$155,568	$210,668
NINR	1	0	1	0	1	0	1	0	$159,480/ $159,480	$159,480	$159,480

NCCAM = National Center for Complementary and Alternative Medicine; NCI = National Cancer Institute; NIDA = National Institute on Drug Abuse; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke; NINR= National Institute of Nursing Research

Table 3. Years between the NIH-funded project end dates and the publication dates of the results

NIH Agency	Interval Time Point	Mean	Minimum	Maximum	Standard Deviation
NCCAM	Project End Date	1.9	1.4	2.4	0.7
NCCAM	Budget End Date	2.4	1.4	3.4	1.4
NIDA	Project End Date	2.3	1.8	2.8	0.7
NIDA	Budget End Date	2.8	1.8	3.8	1.4
NINDS	Project End Date	2.3	0.6	3.7	1.6
NINDS	Budget End Date	3.0	1.6	4.7	1.6

NCCAM = National Center for Complementary and Alternative Medicine; NIDA = National Institute on Drug Abuse; NIMH = National Institute of Mental Health; NINDS = National Institute of Neurological Disorders and Stroke

Table 4. Publication and posting of the results of migraine prevention studies registered in ClinicalTrials.gov

		Published	Not Published	Total	% Published	Has Results	No Results Available	Total	% Posted
Category	Total	14	53	67	20.9	9	58	67	13.4
Age	Adult	8	29	37	21.6	6	31	37	16.2
Age	Adult| Senior	3	18	21	14.3	3	18	21	14.3
Age	Child	0	6	6	0.0	0	6	6	0.0
Age	Child| Adult	3	0	3	100.0	0	3	3	0.0
Gender	Both	13	46	59	22.0	9	50	59	15.3
Gender	Female	0	1	1	0.0	0	1	1	0.0
Type	Interventional	14	51	65	21.5	9	56	65	13.8
Type	Observational	0	2	2	0.0	0	2	2	0.0
Intervention	Behavioral	0	1	1	0.0	0	1	1	0.0
Intervention	Biological	2	2	4	50.0	2	2	4	50.0
Intervention	Drug	11	50	61	18.0	7	54	61	11.5
Intervention	Procedure	1	0	1	100.0	0	1	1	0.0
Phases	Phase 1|Phase 2	0	1	1	0.0	0	1	1	0.0
Phases	Phase 2	2	17	19	10.5	2	17	19	10.5
Phases	Phase 2|Phase 3	0	1	1	0.0	0	1	1	0.0
Phases	Phase 3	8	16	24	33.3	3	21	24	12.5
Phases	Phase 4	2	5	7	28.6	2	5	7	28.6
Phases	Phase 1	0	1	1	0.0	0	1	1	0.0
Phases	Phase 2I	0	3	3	0.0	0	3	3	0.0
Phases	Phase 4	1	1	2	50.0	0	2	2	0.0
Placebo	No	3	21	24	12.5	2	22	24	8.3
Placebo	Yes	11	32	43	25.6	7	36	43	16.3
Recruitment	Active, not recruiting	0	2	2	0.0	0	2	2	0.0
Recruitment	Completed	13	34	47	27.7	8	39	47	17.0
Recruitment	Not yet recruiting	0	2	2	0.0	0	2	2	0.0
Recruitment	Recruiting	1	9	10	10.0	0	10	10	0.0
Recruitment	Terminated	0	4	4	0.0	1	3	4	25.0
Recruitment	Withdrawn	0	2	2	0.0	0	2	2	0.0
Reason for termination	Administrative	0	1	1	0.0	1	0	1	100.0
Reason for termination	Other	0	1	1	0.0	0	1	1	0.0
Reason for termination	Safety related	0	2	2	0.0	0	2	2	0.0
Funding	Industry	9	34	43	20.9	4	39	43	9.3
Funding	Industry|NIH	0	1	1	0.0	1	0	1	100.0
Funding	Industry|Other	1	1	2	50.0	0	2	2	0.0

Table 4. Publication and posting of the results of migraine prevention studies registered in ClinicalTrials.gov (continued)

		Published	Not Published	Total	% Published	Has Results	No Results Available	Total	% Posted
Funding	Other	1	8	9	11.1	0	9	9	0.0
Funding	Other|Industry	2	6	8	25.0	3	5	8	37.5
Funding	Other|NIH	0	1	1	0.0	0	1	1	0.0
Funding	Other|NIH|Industry	1	0	1	100.0	1	0	1	100.0
Funding	Other|U.S. Fed|Industry	0	1	1	0.0	0	1	1	0.0
Funding	U.S. Fed|Other	0	1	1	0.0	0	1	1	0.0

Table 5. Odds of publication and posting of results in ClinicalTrials.gov among all studies registered in ClinicalTrials.gov

Outcome	Active	Control	Active With Outcome	Active Without Outcome	Control With Outcome	Control Without Outcome	Odds Ratio	Lower 95% CI	Upper 95% CI
Publication	Interventional	Observational	14	51	0	2	1.41	0.06	30.99
Publication	Drug studies	All other studies	11	50	3	3	0.22	0.04	1.24
Publication	Placebo control	No placebo control (active treatments comparison)	11	32	3	21	2.41	0.60	9.66
Publication	Has results	No results available	4	5	10	48	3.84	0.87	16.88
Publication	Funded by industry	Funded by other sources	9	34	1	10	2.65	0.30	23.49
Posting results	Drug studies	All other studies	7	54	2	4	0.26	0.04	1.68
Posting results	Phase 3-4 trials	Phase 1-2 trials	5	28	2	23	2.05	0.36	11.58
Posting results	Placebo control	No placebo control (active treatments comparison)	7	36	2	22	2.14	0.41	11.23
Posting results	Terminated for safety reasons	Terminated for other reasons	0	2	1	1	0.20	0.00	8.82
Posting results	Funded by Industry	Funded by other sources	9	47	0	11	4.60	0.25	84.94

Abstracted data are available in Appendix D with evidence tables (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy). Randomized trials examined 59 drugs from 14 pharmacologic 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 D2).

Applicability

The results from eligible studies were applicable to the target population. Most RCTs were conducted in the United States and Western countries and used the International Headache Society's definition (Appendix Table D3). Older publications used the definition of migraine developed by the Ad Hoc Committee on Classification of Headache, and about 34 RCTs did not specify a migraine definition.

Investigators recruited patients in clinics in almost half of RCTs. Half did not report this information, and eight RCTS clearly indicated community-based recruitment. RCTs enrolled an average of 210 adults, measured the outcomes at 2 to 3 months of followup, and reported about 14 percent loss of followup (Table 6 and Appendix Table D4).

Studies enrolled mostly adults (average age, 38 years) and adolescents (Table 7). Women made up the majority of enrolled subjects (Appendix Table D5). Few trials reported a proportion of obese subjects, but many participants were overweight according to the average body mass index. Most trials included patients with and without aura (Appendix Table D5). Enrolled patients had an average of five monthly migraine attacks. Almost half of the enrolled subjects were naïve to migraine preventive drugs (Table 7). Patient age and baseline migraine characteristics were similar in most trials (Appendix Table D6).

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

Risk of Bias

More than half of the RCTs had medium risk of bias and about 21 percent had low risk of bias (Table 8). Proportions of RCTs with low risk of bias varied among drugs (Appendix Table D7). Among approved drugs, the percent of low-risk-of-bias RCTs was as follows: topiramate, 45 percent; divalproex, 67 percent; and propranolol, 13 percent (Appendix Table D7). Most RCTs (86 percent) were double blind. Timolol was examined in two RCTs of medium risk of bias. We concluded unclear adequacy of allocation concealment in 94 percent of RCTs and adequacy of randomization in 51 percent of RCTs (Table 8). Planned intention to treat was reported in 24 percent of RCTs.

Published RCTs rarely presented subject flows. Nor did RCTs report why some eligible subjects were not randomized and therefore excluded from the trials. 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.

Table 6. Total number randomized, weeks of followup, and loss of followup in randomized controlled clinical trials of migraine prevention in adults

	Total Sample	# RCTs That Reported Sample	Sample Assigned to Treatment Mean [Min to Max]	# RCTs That Reported Length of Followup	Total Length of Followup, Weeks Mean [Min to Max]	# RCTs That Reported % Loss of Followup	% Loss of Followup Mean [Min to Max]
Antiepileptics	7656	42	182.3 [23 to 818]	43	17.6 [8.0 to 28.0]	28	5.5 [0.0 to 36.0]
Antidepressants	1701	21	83.0 [17 to 391]	21	13.5 [4.0 to 27.0]	19	22.6 [0.0 to 48.0]
Beta blockers	6006	62	96.9 [14 to 810]	65	18.1 [4.0 to 60.0]	36	12.3 [0.0 to 37.5]
ACE inhibitors	72	2	36.0 [12 to 60]	2	37.8 [7.5 to 68.0]	1	22.0
Angiotensin II receptor blockers	144	2	72.0 [60 to 84]	2	22.0 [12.0 to 32.0]	2	11.0 [5.0 to 17.0]
Calcium channel blockers	2602	33	78.8 [20 to 521]	33	18.8 [8.0 to 36.0]	30	15.4 [0.0 to 48.3]
Antiadrenergics	711	15	47.4 [20 to 133]	15	21.6 [8.0 to 48.0]	11	21.2 [6.0 to 38.0]
Dopaminergic agents	172	3	57.3 [30 to 102]	3	28.0 [16.0 to 40.0]		Not reported
Ergot alkaloids	1040	9	115.6 [18 to 384]	9	13.6 [6.0 to 24.0]	8	11.6 [0.0 to 32.4]
NSAIDs	23993	16	1499.6 [26 to 22071]	16	26.0 [4.0 to 144.0]	6	15.2 [0.0 to 29.6]
Magnesium	174	3	58.0 [24 to 81]	3	17.3 [12.0 to 24.0]	3	23.0 [11.0 to 42.0]
Nondrugs vs. drugs	632	4	158.0 [114 to 218]	4	20.0 [16.0 to 24.0]		Not reported
Cortical spreading depression inhibitor	124	1	124.0	1	13.0	1	5.1
Muscle relaxants	136	1	136.0	1	12.0		Not reported
Montelukast	177	1	177.0	1	20.0	1	2.2
Total	45340	215	210.9 [12 to 22071]	219	18.6 [4.0 to 144.0]	146	13.9 [0.0 to 48.3]
% RCTs that did not report the variable		2.3		0.5		33.6	

ACE = angiotensin converting enzyme; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized clinical trial

Table 7. Reporting of patient baseline characteristics in randomized controlled clinical trials of migraine prevention drugs in adults

Drugs	# RCTs	Age Mean [Min to Max]	# RCTs	% Female, Mean [Min to Max]	# RCTs	Obesity, BMI Mean [Min to Max]	# RCTs	Baseline Frequency of Migraine/Month Mean [Min to Max]	# RCTs	Duration of Migraine, Years Mean [Min to Max]	# RCTs	% With Aura Mean [Min to Max]	# RCTs	% Naïve to Treatment Mean [Min to Max]
Anti-epileptics	39	39.2 [29.4 to 46.0]	41	76.3 [10.9 to 100.0]	8	27.1 [23.0 to 30.3]	40	6.5 [1.0 to 26.6]	14	13.2 [3.0 to 25.0]	18	24.0 [0.0 to 86.3]	7	43.0 [0.0 to 100.0]
Anti-depressants	17	36.6 [31.0 to 44.4]	19	80.0 [63.5 to 92.3]		Not reported	2	6.0 [5.0 to 7.0]	2	18.4 [16.0 to 20.8]	8	19.2 [0.0 to 45.2]	2	66.7 [0.0 to 100.0]
Beta blockers	50	37.8 [28.6 to 43.5]	61	78.5 [52.0 to 94.5]	2	23.1 [22.8 to 23.4]	44	4.5 [2.0 to 8.4]	27	16.8 [9.0 to 26.0]	46	39.8 [0.0 to 100.0]	7	53.8 [0.0 to 93.2]
ACE inhibitors	2	45.0 [41.0 to 49.0]	2	69.5 [58.0 to 81.0]		Not reported	1	2.3		Not reported		Not reported		Not reported
Angiotensin II receptor blockers	2	40.9 [39.8 to 42.0]	2	81.8 [79.0 to 84.5]	1	24.0	1	6.2		0.0		Not reported		Not reported
Calcium channel blockers	28	35.5 [29.0 to 44.0]	32	73.8 [41.0 to 91.1]	2	23.4 [23.0 to 23.7]	22	5.2 [2.0 to 10.0]	18	14.1 [5.0 to 20.0]	29	25.3 [0.0 to 100.0]	6	54.5 [25.0 to 100.0]
Anti-adrenergics	12	37.8 [32.0 to 48.0]	14	77.4 [30.0 to 92.0]		Not reported	5	5.1 [4.0 to 6.5]	3	16.0 [12.0 to 22.0]		Not reported		Not reported
Dopa-minergic agents	2	34.3 [33.9 to 34.6]	3	74.4 [71.6 to 76.7]		Not reported	3	5.3 [4.3 to 6.0]		Not reported	3	0.0 [0.0 to 0.0]		Not reported
Ergot alkaloids	7	35.9 [30.0 to 42.0]	8	76.3 [60.0 to 95.0]	2	23.7 [23.1 to 24.2]	6	4.8 [3.0 to 8.5]	5	16.2 [14.2 to 20.0]	7	23.1 [0.0 to 67.5]	2	63.3 [60.0 to 66.7]
NSAIDs	15	39.5 [35.0 to 53.2]	15	73.9 [0.0 to 100.0]	2	25.6 [25.0 to 26.1]	6	4.7 [1.3 to 8.2]	4	17.2 [15.0 to 20.0]	2	4.4 [0.0 to 8.7]		Not reported
Magnesium	2	42.4 [41.0 to 43.8]	2	89.5 [86.0 to 93.0]		Not reported	2	5.0 [4.0 to 6.0]	1	4.2	2	50.0 [0.0 to 100.0]		Not reported

Table 7. Reporting of patient baseline characteristics in randomized controlled clinical trials of migraine prevention drugs in adults (continued)

Drugs	# RCTs	Age Mean [Min to Max]	# RCTs	% Female, Mean [Min to Max]	# RCTs	Obesity, BMI Mean [Min to Max]	# RCTs	Baseline Frequency of Migraine/Month Mean [Min to Max]	# RCTs	Duration of Migraine, Years Mean [Min to Max]	# RCTs	% With Aura Mean [Min to Max]	# RCTs	% Naïve to Treatment Mean [Min to Max]
Nondrug vs. drugs	4	38.9 [37.8 to 40.1]	4	87.9 [78.9 to 100.0]	1	23.5	3	4.7 [2.0 to 6.3]	1	15.9	3	38.9 [0.0 to 100.0]	1	46.5 [0.0 to 0.0]
Cortical spreading depression inhibitor	1	36.0	1	92.3		Not reported		Not reported		Not reported		Not reported	1	100.0
Muscle relaxants	1	40.3	1	79.0		Not reported		Not reported		Not reported		Not reported		Not reported
Montelukast	1	40.0	1	88.0		Not reported	1	5.1 [0.0 to 0.0]		Not reported		Not reported		Not reported
Total	183	37.9 [28.6 to 53.2]	206	77.2 [0.0 to 100.0]	18	25.3 [22.8 to 30.3]	136	5.3 [1.0 to 26.6]	75	15.3 [3.0 to 26.0]	118	30.0 [0.0 to 100.0]	26	53.0 [0.0 to 100.0]
%RCTs that did not report the variable	17		6		92		38		66		46		88	

ACE = angiotensin converting enzyme; BMI = body mass index; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized clinical trial

Table 8. Number of randomized controlled clinical trials of migraine prevention in adults that met risk of bias criteria

Drug Classes	Double Blind	Open Label	Single Blind	Adequate Allocation Conceal-ment	Unclear Allocation Conceal-ment	Adequate Randomi-zation	Not Adequate Randomi-zation	Unclear Adequacy of Randomi-zation	Planned Intention to Treat Analysis	Low Risk of Bias	Medium Risk of Bias	High Risk of Bias	Unclear Risk of Bias	Total
Anti-epileptics	40	3	0	9	34	23	6	14	23	19	22	2	0	43
Anti-depressants	19	3	0	0	22	14	3	5	3	1	18	3	0	22
Beta blockers	59	4	2	1	64	18	2	45	11	8	52	5	0	65
ACE inhibitors	2	0	0	1	1	0	0	2	1	2	0	0	0	2
Angiotensin II receptor blockers	2	0	0	1	1	0	1	1	1	1	0	1	0	2
Calcium channel blockers	29	3	2	0	34	15	4	15	3	2	24	8	0	34
Anti-adrenergics	14	1	0	0	15	1	0	14	1	4	9	1	1	15
Dopa-minergic agents	3	0	0	0	3	0	1	2	0	0	2	1	0	3
Ergot alkaloids	8	1	0	0	9	4	0	5	1	1	8	0	0	9
Muscle relaxants	1	0	0	0	1	1	0	0	0	0	1	0	0	1
Montelukast	1	0	0	0	1	1	0	0	1	1	0	0	0	1
NSAIDs	7	9	0	0	16	5	3	8	3	3	10	2	1	16
Magnesium	3	0	0	0	3	2	1	0	2	2	0	1	0	3
Nondrugs compared with drugs	0	3	1	2	2	3	1	0	3	1	2	1	0	4
Total	188	27	5	14	206	87	22	111	53	45	148	25	2	220
Percent	85.5	12.3	2.3	6.4	93.6	39.5	10.0	50.5	24.1	20.5	67.3	11.4	0.9	

ACE = angiotensin converting enzyme; NSAID = nonsteroidal anti-inflammatory drug

Key Question 1. What is the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in adults?

Results from RCTs were available in 245 references. RCTs examined four approved drugs for episodic migraine (topiramate, divalproex, propranolol, and timolol), one approved drug for chronic migraine (onabotulinumtoxin A), and various off-label preventive drugs. Most trials examined a monotherapy with one active agent compared with placebo or to another drug. RCTs rarely reported exact drugs and doses of concomitant treatments. However, we surmise there were no concomitant treatments because most trials disallowed concomitant drugs during the run-in period and after randomization. Strength of evidence was low due to medium or high risk of bias and imprecise estimates from individual or meta-analyzed RCTs.

KQ1a. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with placebo or no active treatment?

All approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent in patients with episodic migraine and baseline <15 migraine days per month (clinical response). The relative effect of drugs was moderate: drugs resulted in clinical response in 200 to 400 patients per 1,000 treated. Clinicians need to treat three to five patients with episodic migraine to prevent half or more migraine attacks in one patient.

Strength of evidence was lowered due to medium risk of bias and imprecise estimates. Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of onabotulinumtoxin A and topiramate (from 50-100 mg/day with no additional benefits with 200 mg/day).

Among off-label drugs, pooled analyses offered low-strength evidence that antiepileptic gabapentin, beta-blocker metoprolol, and calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by ≥50 percent. Individual RCTs offered low-strength evidence that off-label beta blockers, acebutolol atenolol and nadolol, were better than placebo in reducing monthly migraine attacks by ≥50 percent. Individual RCTs demonstrated that the angiotensin converting enzyme inhibitors captopril and lisinopril and the angiotensin II antagonist candesartan were better than placebo in reducing monthly migraine attacks by ≥50 percent.

We present strength of evidence for patient-centered outcomes, including complete migraine cessation (Table 9) and migraine prevention with approved (Table 10) and off-label drugs (Tables 11 and 12).

Only a few RCTs examined quality of life, and they provided no consistent evidence of improvement with examined drugs. The studies rarely assess clinical importance of the changes in quality of life or disability scales. We describe those effects as well as changes in intermediate outcomes in the text and appendix tables.

Table 9. 100% reduction in monthly migraine frequency with pharmacologic preventive treatments versus placebo in adults with episodic migraine, results from randomized controlled clinical trials

Active Drug, Weeks From Randomization to Time to Measure Outcome	References	Sample	% With Outcome in Active [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Topiramate, 16-26 weeks	Pooled Bussone, 2005[84] Silberstein 2006[85] Silberstein, 2009[86]	1299	5.1 [2.6]	1.9 (1.0 to 3.4)	0.02 (-0.01 to 0.05)	NS	NS	Medium	Yes	No	No	Low
	p value			0.499	0.067							
	I squared			0.00%	63.00%							
Gabapentin 17 weeks of treatment	NCT00742209, 2010[87]	82	25.8 [20.9]	1.3 (0.5 to 3.4)	0.06 (-0.15 to 0.26)	NS	NS	Low	Yes	Not applicable	Imprecise	Low
Captopril 32 weeks of treatment	**Minervini, 1987[88]**	**24**	**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)**	**Low**	**Yes**	**Not applicable**	**Imprecise**	**Low**
Nimodipine 12 weeks of treatment	**Gelmers, 1983[89]**	**60**	**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)**	**Medium**	**Yes**	**Not applicable**	**Imprecise**	**Low**
Dihydro-ergotamine 20 weeks of treatment	Pradalier, 2004[90]	384	37.5 [30.0]	1.3 (0.9 to 1.7)	0.08 (-0.02 to 0.17)	NS	NS	Low	Yes	Not applicable	Imprecise	Low
Indomethacin 4 weeks of treatment	Anthony, 1968[91]	38	5.3 [10.5]	0.5 (0.0 to 5.1)	-0.05 (-0.22 to 0.12)	NS	NS	Medium	Yes	Not applicable	Imprecise	Low

Bold = significant differences when 95% CI of absolute risk differences do not include 0; CI = confidence interval; NS = not significant;
Number needed to treat and number of attributable events were calculated for statistically significant differences

Table 10. Migraine prevention with approved pharmacologic treatments versus placebo in adults, results from randomized controlled clinical trials (pooled with random effects models)

Active Drug	References	Sample	% With Outcome With Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Chronic Migraine												
Onabotulinumtoxin A ≥50% decrease in migraine frequency	**Pooled[92-94]**	**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)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	p value			0.7	0.9							
	I squared			0.00%	0.00%							
Episodic Migraine												
Topiramate 100% reduction in migraine frequency	Pooled[84-86]	1299	5.1 [2.6]	1.9 (1.0 to 3.4)	0.02 (-0.01 to 0.05)	NS	NS	Medium	Yes	No	No	Low
	p value			0.499	0.067							
	I squared			0.00	0.63							
Topiramate on >50% reduction on migraine frequency	**Pooled[84,85, 95-99]**	**1422**	**49.6 [25.1]**	**2.0 (1.5 to 2.7)**	**0.29 (0.18 to 0.40)**	**3 (3 to 6)**	**288 (176 to 400)**	**Medium**	**Yes**	**Yes**	**Yes**	**Moderate**
	P value			0.036	0.001							
	I squared			0.555	0.736							
Topiramate on >50% reduction on migraine days	**Pooled[84,86, 100]**	**1145**	**42.2 [23.3]**	**1.7 (1.0 to 2.9)**	**0.18 (0.08 to 0.28)**	**6 (4 to 13)**	**179 (75 to 284)**	**Low**	**Yes**	**Yes**	**No**	**Moderate**
	P value			0.012	0.042							
	I squared			0.772	0.684							
Topiramate on ≥75% reduction in migraine days	**Pooled[84,86]**	**1086**	**22.3 [11.0]**	**1.9 (1.1 to 3.1)**	**0.10 (-0.01 to 0.20)**	**NS**	**NS**	**Low**	**Yes**	**Yes**	**No**	**Moderate**
	P value			0.123	0.026							
	I squared			0.58	0.797							
Divalproex	**Pooled[101-103]**	**405**	**43.0 [23.3]**	**2.2 (1.1 to 4.2)**	**0.24 (0.10 to 0.38)**	**4 (3 to 10)**	**241 97 to 384)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	P value			0.123	0.098							
	I squared			0.523	0.569							

Table 10. Migraine prevention with approved pharmacologic treatments versus placebo in adults, results from randomized controlled clinical trials (pooled with random effects models) (continued)

Active Drug	References	Sample	% With Outcome With Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Propranolol	**Pooled[104-107]**	**541**	**45.1 [22.3]**	**2.0 (1.5 to 2.7)**	**0.22 (0.14 to 0.30)**	**4 (3 to 7)**	**223 (142 to 304)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	P value			0.995	0.936							
	I squared			0	0							
Timolol 100% reduction in migraine frequency	Single RCT[108]	28	14.3 [0.0]	5.0 (0.3 to 95.6)	0.14 (-0.07 to 0.35)	NS	NS	Medium	Yes	Not applicable	No	Low
Timolol ≥50% reduction in migraine frequency	**Pooled[104, 107,109]**	**276**	**49.4 [23.3]**	**2.1 (1.5 to 3.1)**	**0.27 (0.15 to 0.38)**	**4 (3 to 6)**	**265 (154 to 377)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	P value			0.732	0.606							
	I squared			0	0							

Bold = significant differences when 95% CI of absolute risk difference do not include 0; CI = confidence interval; RCT = randomized controlled trial; NS = not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Table 11. Migraine prevention with pharmacologic treatments versus placebo in adults with episodic migraine (pooled with random effects model results from randomized controlled clinical trials)

Active Drug	References	Sample	% With Outcome With Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Gabapentin	**Pooled[87,110,111]**	**270**	**45.9 [31.0]**	**1.5 (1.1 to 2.0)**	**0.17 (0.06 to 0.27)**	**6 (4 to 16)**	**165 (61 to 269)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	P value			**0.487**	**0.847**							
	I squared			**0**	**0**							
Metoprolol	**Pooled[89,112-114]**	**225**	**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)**	**Medium**	**Yes**	**Yes**	**No**	**Low**
	P value			**0.415**	**0.385**							
	I squared			**0**	**0**							
Nimodipine	**Pooled[89,112]**	**126**	**28.6 [6.3]**	**4.5 (0.5 to 40.1)**	**0.23 (0.06 to 0.39)**	**4 (3 to 16)**	**229 (64 to 394)**	**Medium**	**Yes**	**No**	**No**	**Low**
	P value			0.125	0.194							
	I squared			0.576	0.407							
Magnesium	Pooled[115,116]	137	33.8 [25.8]	1.3 (0.7 to 2.3)	0.08 (-0.09 to 0.26)	NS	NS	Low	Yes	No	No	Low
	P value			0.268	0.248							
	I squared			0.186	0.251							

CI = confidence interval; NS= not significant

Number needed to treat and number of attributable events were calculated for statistically significant differences

Bold = significant differences when 95% CI of absolute risk difference do not include 0.

Table 12. Migraine prevention (50% or more reduction) with off-label pharmacologic treatments versus placebo in adults with episodic migraine, results from individual randomized controlled clinical trials

Active Drug, Weeks From Randomization to Time to Measure Outcome	Reference	Sample	% With Outcome With Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Acetazolamide 12 weeks	Vahedi, 2002[117]	53	30.8 [33.3]	0.9 (0.4 to 2.0)	-0.03 (-0.28 to 0.23)	NS	NS	Low	Yes	NA	Imprecise	Low
Carbamazepin 6 weeks	**Rompel, 1970[118]**	**96**	**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)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Lamotrigine 20 weeks	Gupta, 2007[99]	120	46.0 [34.0]	1.4 (0.9 to 2.2)	0.13 (-0.04 to 0.31)	NS	NS	Low	Yes	NA	Imprecise	Low
Oxcarbazepine 15 weeks	Silberstein, 2008[119]	170	32.9 [36.5]	0.9 (0.6 to 1.4)	-0.04 (-0.18 to 0.11)	NS	NS	Low	Yes	NA	Imprecise	Low
Valproate 12 weeks	**Jensen, 1994[120]**	**86**	**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)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Acebutolol 12 weeks	**Nanda, 1978[121]**	**86**	**30.2 [4.7]**	**6.5 (1.6 to 27.1)**	**0.26 (0.10 to 0.41)**	**4 (2 to 10)**	**256 (105 to 407)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Alprenolol 6 weeks	Ekbom, 1975[122]	66	33.3 [36.4]	0.9 (0.5 to 1.8)	-0.03 (-0.26 to 0.20)	NS	NS	Medium	Yes	NA	Imprecise	Low
Atenolol 12 weeks	**Forssman, 1983[123]**	**48**	**33.3 [0.0]**	**17.0 (1.0 to 278.9)**	**0.33 (0.14 to 0.53)**	**3 (2 to 7)**	**333 (140 to 527)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Nadolol 12 weeks	**Freitag, 1984[124]**	**32**	**25.0 [0.0]**	**4.7 (0.3 to 75.0)**	**0.25 (0.02 to 0.48)**	**4 (2 to 45)**	**250 (22 to 478)**	**Low**	**Yes**	**NA**	**Imprecise**	**Low**
Amitriptyline 16 weeks	Couch, 2011[125]	391	24.2 [24.4]	1.0 (0.7 to 1.4)	0.00 (-0.09 to 0.08)	NS	NS	Medium	Yes	NA	Imprecise	Low
Amitriptyline 4 weeks (≥75% improvement in headache)	**Couch, 1976[126]**	**73**	**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)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Tonabersat 12 weeks	Goadsby, 2009[127]	124	40.7 [36.9]	1.1 (0.7 to 1.7)	0.04 (-0.13 to 0.21)	NS	NS	Low	Yes	NA	Imprecise	Low
Lisinopril 12 weeks	Schrader, 2001[128]	120	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)	Low	Yes	NA	Imprecise	Low
Candesartan 12 weeks	Tronvik, 2003[129]	120	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)	Low	Yes	NA	Imprecise	Low

Table 12. Migraine prevention (50% or more reduction) with off-label pharmacologic treatments versus placebo in adults with episodic migraine, results from individual randomized controlled clinical trials (continued)

Active Drug, Weeks From Randomization to Time to Measure Outcome	Reference	Sample	% With Outcome With Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Nifedipine 4 weeks	Shukla, 1995[130]	72	55.6 [11.1]	5.0 (1.9 to 13.2)	0.44 (0.25 to 0.64)	2 (2 to 4)	444 (252 to 637)	Medium	Yes	NA	Imprecise	Low
Dihydro-ergotamine 20 weeks	Pradalier, 2004[90]	384	60.9 [56.0]	1.1 (0.9 to 1.3)	0.05 (-0.05 to 0.15)	NS	NS	Low	Yes	NA	Imprecise	Low
Lisuride 12 weeks	Somerville, 1976[131]	150	37.3 [25.3]	1.5 (0.9 to 2.4)	0.12 (-0.03 to 0.27)	NS	NS	Medium	Yes	NA	Imprecise	Low
Flurbiprofen 8 weeks	Solomon, 1993[132]	46	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)	Medium	Yes	NA	Imprecise	Low
Indomethacin 4 weeks	Anthony, 1968[91]	38	31.6 [26.3]	1.2 (0.4 to 3.3)	0.05 (-0.24 to 0.34)	NS	NS	Medium	Yes	NA	Imprecise	Low
Rofecoxib 12 weeks	Visser, 2004[133]	175	22.0 [9.5]	2.3 (1.1 to 5.0)	0.12 (0.02 to 0.23)	8 (4 to 53)	125 (19 to 230)	Medium	Yes	NA	Imprecise	Low
Tolfenamic Acid 10 weeks	Mikkelsen, 1982[134]	62	45.2 [6.5]	7.0 (1.7 to 28.3)	0.39 (0.19 to 0.58)	3 (2 to 5)	387 (192 to 582)	Medium	Yes	NA	Imprecise	Low
Aspirin 240 weeks (ever having migraine attack)	Buring, 1990[135]	22071	6.0 [7.4]	0.8 (0.7 to 0.9)	-0.01 (-0.02 to -0.01)	-70 (48 to 131)	-14 (8 to 21)	Low	Yes	NA	Imprecise	Low
Montelukast 12 weeks	Brandes, 2004[136]	177	24.2 [21.8]	1.2 (0.7 to 2.0)	0.0 (-0.09 to 0.16)	NS	NS	Low	Yes	NA	Imprecise	Low

CI = confidence interval; NA = Not applicable; NS= not significant

Number needed to treat and number of attributable events were calculated for statistically significant differences

Bold = significant differences when 95% CI of absolute risk difference do not include 0.

Prevention of Chronic Migraine

Muscle Relaxants

Onabotulinumtoxin A

We identified 15 RCTs that examined the efficacy of botulinum toxin for migraine prevention; 13 RCTs examined onabotulinumtoxin A and two RCTs examined abobotulinumtoxin A (Appendix Table D8). The studies enrolled an average of 285 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 made up 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 (Appendix Table D9). All RCTs were double blind and most had low risk of bias (Appendix Table D10).

Onabotulinumtoxin A was better than placebo in reducing monthly migraine attacks by ≥50 percent (three RCTs of 459 adults, low-strength evidence) (Appendix Table D11).[92-94] Onabotulinumtoxin A tended to increase the likelihood of ≥50 percent reduction in migraine frequency compared with placebo in all RCTs (Appendix Table D12). Pooled relative increase by 50 percent achieved statistical significance (pooled RR 1.5, 95% CI, 1.2 to 1.8). Pooled analyses demonstrated that 170 adults per 1,000 treated (95% CI, 82 to 258) would experience ≥50 percent reduction in migraine frequency with onabotulinumtoxin A (Table 10). No RCTs of abobotulinumtoxin A reported rates of ≥50 percent reduction in monthly migraine attacks.

A reduction in migraine days was considered as a primary outcome in the Phase III Research Evaluating Migraine Prophylaxis Therapy (PREEMPT) RCT that reported statistically significant reduction in frequency of headache days relative to 20 headache days at baseline (-9.0 days with onabotulinumtoxin A versus -6.7 days with placebo, $p < .001$).[137] The same trial reported a statistically significant reduction in frequency of migraine days relative to 19 migraine days at baseline (mean difference with placebo -2.4 with 95% CI -3.3 to -1.4).[137] We could not pool the results from other RCTs that examined a reduction in migraine days or hours because the trials failed to report data needed for reproducible results.[137-139]

For intermediate outcomes, the absolute number of migraine attacks did not differ between onabotulinumtoxin A and placebo (Appendix Table D13). Improvement in migraine severity was inconsistent across four RCTs (Appendix Table D14).[92,139-141] Improvement in migraine disability assessment was inconsistent across two RCTs (Appendix Table D14).[93,142] 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 D14).[142] The PREEMPT clinical program RCT demonstrated statistically significant improvement in all domains of the Migraine-Specific Quality of Life Questionnaire.[143] Significant improvement was demonstrated in global assessment, severity of migraine symptoms, self-management of migraine, and ability to work and participate in recreational activities (Appendix Table D14).[142]

In our separate analysis of RCTs of abobotulinumtoxin A we found inconsistent effects on patient global evaluation of treatment success. The Dysport Migraine Study Group reported a statistically significant increase in patient's global evaluation of treatment efficacy.[144] Slightly or much improved migraine frequency was reported in 281 patients per 1,000 treated (95% CI 46 to 516).[144] In contrast, the Dysport® In Migraine Without Aura Prophylaxis trial found no

differences in patient or investigators' perception of global assessment with the active drug versus placebo.[139] Neither trial showed statistically significant reduction in absolute number of migraine attacks with abobotulinumtoxin A versus placebo.[139,144]

Tizanidine

Tizanidine was better than placebo in reducing migraine severity (one RCT of 136 adults) but had no effect on migraine frequency.[145]

Antiepileptics

The Topiramate Chronic Migraine Study Group RCT offered low-strength evidence that topiramate was better than placebo in reducing from baseline monthly migraine days, rates of 25 percent reduction in monthly migraine attacks, and frequency of associated symptoms.[86,146,147] Topiramate was not better than placebo in reducing monthly migraine attacks by≥50 percent.[86] Topiramate did not decrease treatment discontinuation due to failure.[146]

The drug improved quality of life and migraine related disability in adult with chronic migraine. We estimated that 133 patients (95% CI, 27 to 239) per 1,000 treated would experience improvement in quality of life measured using the SGIC instrument (Subject's Global Impression of Change). We estimated that 72 patients (95% CI, 7 to 137) per 1,000 treated experienced reduction in migraine related disability.[147] Improvement in disability scale score was large and clinically important.[100]

Prevention of Episodic Migraine

Antiepileptics

Topiramate

Individual RCTs and two pooled analyses of individual patient data from RCTs examined efficacy of topiramate versus placebo for migraine prevention in adults **(**Appendix Table D15). Most trials were funded by industry (Appendix Table D16). All trials were double blind and most had low risk of bias (Appendix Table D17).

Topiramate was not better than placebo in achieving complete cessation of migraine (Table 9).[84-86] Topiramate in doses of 50, 100, or 200 mg/day was better than placebo in reducing monthly migraine frequency by≥50 percent (Table 10 and Appendix Table D18). The results were consistent across the studies and robust regardless of pooling methods (Appendix Table D19). Topiramate was also better than placebo in reducing monthly migraine days by≥50 percent (Table 10). Topiramate tended to reduce treatment discontinuation due to lack of efficacy with borderline statistical significance in pooled analyses (pooled absolute risk difference -0.04 95% CI -0.07 to 0).[84,85,96,99,146,148-150]

Topiramate, 100 mg/day, decreased the absolute number of migraine days by 5 days/month in pooled analyses of RCTs (Appendix Table D20). The reduction in migraine severity scores was inconsistent across the studies (Appendix Table D21). Individual RCTs demonstrated significant improvement in quality of life as measured by scores on the Headache Impact Test,[149] Migraine Specific Questionnaire,[151] and Migraine Disability Assessment[100] (Appendix Table D22). Topiramate was better than placebo in improving general health status in a previously published pooled analysis of individual patient data from RCTs (Appendix Table D23).[152] 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 pain and general health (Appendix Table D23).[152]

Topiramate was better than placebo in reducing use of acute drugs (Appendix Table D24). 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 D24).

Divalproex

Three RCTs examined the efficacy of divalproex for migraine prevention in adults (Appendix Table D25).[101-103] All three RCTs were funded by industry (Appendix Table D26) and all were double blind (Appendix Table D27).

Divalproex was better than placebo in reducing monthly migraine frequency by≥50 percent (Table 10 and Appendix Table D28).[101,102] A larger dose of divalproex (1500 mg/day) was effective in achieving a ≥50 percent reduction in migraine-related effects, including impairment of usual activities, need for symptomatic medication, and nausea, vomiting, phonophobia, or photophobia (Appendix Table D29).[103] Evidence was low-strength due to imprecise treatment effects.[103]

Valproate

Small RCTs examined the efficacy of valproate for migraine prevention in adults (Appendix Table D25).[120,153] The trials were double blind and had medium risk of bias because the investigators did not use planned intention-to-treat principles (Appendix Table D27).

Valproate was better than placebo in reducing monthly migraine frequency by ≥50 percent (Table 12).[120] We estimated that 256 patients per 1,000 treated (95% CI, 77 to 435) would experience clinically important reduction in migraine attacks attributable to valproate.[120] Valproate decreased the frequency of migraine attacks and severe attacks,[153] duration of attacks,[153] and the use of drugs for acute attacks[120] (Appendix Table D30).

Beta Blockers

Propranolol

Most RCTs that examined the efficacy of propranolol versus placebo for migraine prevention in adults (Appendix Table D31) failed to report funding sources (Appendix Table D32). All trials were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D33).

Propranolol was better than placebo in reducing migraine monthly frequency by ≥50 percent (Table 10 and Appendix Table D34). The preventive effects of propranolol were consistent across the studies (Appendix Table D35). Propranolol caused a small but significant decrease in the absolute number of monthly migraine attacks (mean difference -1, 95% CI, -2 to -0.3).[104, 105, 154,155] A single RCT demonstrated that propranolol decreased use of drugs for acute attacks, both analgesics (mean difference -0.3, 95% CI, -0.4 to -0.1 doses per patient day) and the acute drug ergotamine (mean difference -0.1, 95% CI, -0.3 to -0.1 doses per patient day).[156]

Timolol

Timolol was not better than placebo in achieving complete migraine cessation (Table 9).[108] Timolol was better than placebo in reducing migraine monthly frequency by ≥50 percent (Table

10 and Appendix Table D36).[104,107,109] Evidence was low-strength due to medium risk of bias and estimate imprecision (Appendix Table D37) Timolol also decreased absolute number of migraine attacks and severity of headaches (Appendix Table D38).

Off-Label Drugs

Off-Label Antiepileptic Drugs

Most RCTs that examined six off-label antiepileptic drugs: acetazolamide, gabapentin, vigabatrin, oxcarbazepine, carbamazepin, and lamotrigine (Appendix Table D39) were sponsored by industry (Appendix Table D40), and all were double blind (Appendix Table D41).

Gabapentin was not better than placebo in achieving complete cessation of migraine attacks (Table 9).[87] Gabapentin was, however, better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 11).[87,110,111] Individual RCTs found that carbamazepin[118] but not oxcarbazepine[119] and acetazolamide[117] were better than placebo in preventing migraine attacks (Table 11).

In addition to off-label antiepileptic drugs examined in RCTs, pregabalin was examined in one open-label uncontrolled trial.[157] 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.[157]

Beta Blockers

Most RCTs that examined the effects of off-label beta blockers versus placebo for migraine prevention in adults (Appendix Table D42) failed to report funding and conflict of interest (Appendix Table D43). All trials were double blind with medium risk of bias because the investigators did not use planned intention-to-treat principles (Appendix Table D44).

Metoprolol

Metoprolol was better than placebo in improving patient perception of marked reduction in migraine attacks (Appendix Tables D45).[113,114] Pooled analysis found a significant increase in the likelihood of a clinical response (Appendix Table D46)[113,114] but no effect on absolute number of migraine attacks (Appendix Table D47).[113,114,158]

Metoprolol reduced severity of migraine attacks in a single RCT (Appendix Table D48).[114] 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 use of analgesics (Appendix Table D47).[113,114]

Atenolol

Atenolol was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 12 and Appendix Table D46).[159] Atenolol significantly reduced use of ergotamine drugs in a single RCT (Appendix Table D46).[159]

Nadolol

Nadolol was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 12).[124] In a single RCT, nadolol improved perceived relief in frequency, intensity, and severity of migraine attacks (Appendix Table D46).[124]

Alprenolol

Alprenolol was not better than placebo in achieving perceived treatment success (Table 12 and Appendix Table D46).[122] Alprenolol did not reduce the absolute number of monthly migraine attacks or Headache Index scores (Appendix Table D47).[122]

Pindolol

Pindolol was not better than placebo in reducing headache indices by ≥50 percent (Appendix Table D48).[160] Pindolol did not reduce the absolute number of monthly migraine attacks or Headache Index scores (Appendix Table D47).[160]

Acebutolol

Acebutolol was better than placebo in achieving patient perception of clinical response (Table 12).[121]

Antidepressants

Most RCTs that examined the effectiveness of off-label antidepressants for migraine prevention in adults (Appendix Table D49) were sponsored by industry (Appendix Table D50). Most trials were double blind with medium risk of bias (Appendix Table D51).

Amitriptyline

Amitriptyline was better than placebo in reducing monthly migraine attacks by ≥75 percent (Table 12).[126] RCTs demonstrated inconsistent improvement in migraine days and intensity.[126,161]

Fluoxetine

Fluoxetine was not better than placebo in achieving an excellent self-reported clinical response.[162] Improvement in pain indexes was inconsistent in RCTs.[162-164]

Venlafaxine

Venlafaxine in a dose of 150 but not 75 mg/day was better than placebo in achieving an excellent self-reported clinical response.[165]

Femoxetine

Femoxetine was not better than placebo in achieving patient satisfaction with treatment effect or migraine frequency and severity.[166-168]

Mianserin

Mianserin was not better than placebo in improving migraine index or reducing migraine frequency.[169]

Cortical Spreading Depression Inhibitor

Tonabersat

Tonabersat (one RCT of 124 adults, low strength of evidence) (Table 12) was not better than placebo in reducing monthly migraine attacks by ≥50 percent.[127]

Calcium Channel Antagonists

Most RCTs that examined calcium channel blockers for migraine prevention in adults (Appendix Table D52) were sponsored by industry and failed to disclose conflict of interest (Appendix Table D53). All trials were double blind, with medium risk of bias (Appendix Table D54).

Nimodipine

Nimodipine was better than placebo in complete cessation of migraine attacks (Table 9)[89] Nimodipine was better than placebo in reducing monthly migraine attacks by ≥50 percent (Table 11).[89,112]

Nicardipine

Nicardipine was better than placebo in reducing migraine intensity and absolute number of migraine attacks.[170]

Verapamil

Verapamil was better than placebo in reducing composite migraine score and achieving patient satisfaction.[171,172] Verapamil also reduced use of drugs for acute attacks.[171]

Angiotensin Converting Enzyme Inhibitors

Two RCTs examined the effects of ACE inhibitors for migraine prevention in adults (Appendix Table D55).[88,128] One industry-funded RCT examined lisinopril (Appendix Table D56).[128] One RCT of captopril reported neither funding source nor conflict of interest.[88] Both trials were double blind with low risk of bias (Appendix Table D57).

Captopril

Captopril was examined in one small RCT that enrolled adults with comorbid hypertension and depressive symptoms for whom drugs had previously failed to prevent migraines.[88] Captopril was better than placebo in achieving complete cessation of migraine (Table 9) and improvement in Headache Index scores by more than 60 percent.[88] The effect was large. We estimated that 667 patients per 1,000 treated experienced no migraine (95% CI, 388 to 946).[88] Captopril was also better than placebo in reducing depression symptoms.[88]

Lisinopril

Lisinopril was better than placebo in reducing migraine days and severity of symptoms in a single RCTs of 60 adults with episodic migraine.[128] Lisinopril also reduced the absolute number of migraine days and body pain measured with SF-36 but did not decrease use of drugs for acute attacks.[128]

Angiotensin II Receptor Antagonists

Two RCTs examined the effects of angiotensin II receptor antagonists for migraine prevention in adults (Appendix Table D55).[129,173] Both trials were funded by industry and reported conflict of interest (Appendix Table D56).[129,173] Both trials were double blind (Appendix Table D57).

Candesartan

Candesartan was better than placebo in achieving ≥50 percent reduction in migraine days, hours, and severity (Table 12).[129] Candesartan also decreased migraine-related disability but had no effect on use of drugs for acute attacks.[129]

Telmisartan

Telmisartan was not better than placebo in reducing monthly migraine days by ≥50 percent.[173] Telmisartan reduced the absolute number of migraine days but had no effect on use of drugs for acute attacks.[173]

Antiadrenergics

Clonidine

Most RCTs that examined clonidine for its effects on migraine prevention in adults (Appendix Table D58) failed to report funding and conflict of interest (Appendix Table D59). Most trials were double blind but did not use intention-to-treat principles (Appendix Table D60).

Clonidine was better than placebo in ≥50 percent reduction in headache index[174] but not in increasing the number of patients considered better according to self-reported global assessment.[175] Clonidine also failed to achieve clinically noticeable reduction in migraine frequency.[176] Clonidine was better than placebo in reducing migraine duration[177] and use of drugs for acute attacks.[178]

Guanfacine

Guanfacine was better than placebo in reducing monthly migraine days and migraine days with nausea or vomiting in one small RCT.[179]

Ergot Alkaloids

All RCTs that examined effectiveness of ergot alkaloids for migraine prevention in adults (Appendix Table D61) failed to report funding and conflict of interest (Appendix Table D62). Most trials were double blind with medium risk of bias (Appendix Table D63).

Dihydroergotamine

Dihydroergotamine was not better than placebo in achieving complete cessation of migraine attacks[90] (Table 9) or in reducing monthly migraine attacks by ≥50 percent (Table 12).[90]

Leukotriene Receptor Antagonists

Montelukast

Montelukast was not better than placebo in reducing monthly migraine attacks by ≥50 percent.[136]

Nonsteroid Anti-Inflammatory Drugs

Individual RCTs demonstrated that aspirin, flurbiprofen, rofecoxib, and tolfenamic acid were better than placebo in reducing migraine frequency by ≥50 percent (Table 12).

Antipsychotic Drugs

Published RCTs did not examine antipsychotic drugs for migraine prevention. Quetiapine was examined in one uncontrolled trial of refractory migraine, defined as migraine that was previously unresponsive to the combination of atenolol, nortriptyline, and flunarizine.[180] Adult patients with <15 days of headache per month who were not overusing drugs for acute attacks were treated with quetiapine (75mg/day) for 10 weeks. Reduction in migraine frequency by ≥50 percent was achieved in 65 percent of the patients.[180] 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).[180]

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.[181,182]

KQ1b. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active pharmacologic treatments?

Individual RCTs provided low-strength direct evidence about the comparative effectiveness of drugs and demonstrated few significant differences. Indirect adjusted analysis demonstrated no differences between approved drugs and greater odds of clinical response with the angiotensin II antagonist candesartan.

Exploratory network Bayesian meta-analyses demonstrated that approved drugs were similarly better than placebo. Among off-label drug classes; however, angiotensin inhibiting drugs demonstrated the largest significant odds of reducing monthly migraine by ≥50 percent.

Approved Drugs

Muscle Relaxants for Chronic Migraine

Onabotulinumtoxin A

Five RCTs of 350 adults examined comparative effectiveness of onabotulinumtoxin A versus other drugs for migraine prevention (Appendix Table D64). Trials enrolled an average of 70±18 patients ages 18 to 65. Subjects experienced 12 to 24 monthly migraine days. Women made up 91 percent of enrollees. Trials were funded by industry[183,184] or grants,[185] with most investigators disclosing conflict of interest (Appendix Table D65). All RCTs but one[185] were double blind, with medium or high risk of bias due to inadequacy of randomization or unplanned intention-to-treat analyses (Appendix Table D66). 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 onabotulinumtoxin A versus topiramate was examined in two RCTs that found no significant differences in likelihood of migraine prevention or improvement in migraine disability assessment (Appendix Table D67).[183,186] Physicians found marked

improvement in migraine frequency more often with topiramate than onabotulinumtoxin A (ARD 0.33, 95% CI, 0.10 to 0.57) (Appendix Table D67).[183] Absolute scores on the Headache Impact Test were significantly better with topiramate than onabotulinumtoxin A;[183] however, use of drugs for acute attacks did not differ between the two.[183]

A single RCT examined the comparative effectiveness of onabotulinumtoxin A versus divalproex sodium and found no differences in migraine prevention with two drugs (Appendix Table D68).[142] Neither did the two drugs differ for absolute number of migraine days or changes in scores from baseline in the migraine Disability Assessment Scores and/or Headache Impact Test.[142]

A single RCT examined the comparative effectiveness of onabotulinumtoxin A versus amitriptyline and found no differences in migraine prevention with the two drugs (Appendix Table D69).[185] Evidence was insufficient due to a high risk of bias in this individual RCT.[185]

Beta Blockers for Chronic Migraine

The National Institute of Neurological Disorders and Stroke Clinical Research Collaboration trial demonstrated no benefits from combined propranolol and topiramate treatment on migraine prevention in adults with chronic migraine for whom previous topiramate monotherapy had failed.[187] Propranolol combined with the antidepressant nortriptyline was no better than propranolol alone or nortriptyline in reducing the number of days with headache by ≥50 percent.[188]

Antiepileptics for Episodic Migraine

Topiramate

Nine RCTs of 872 adults examined the comparative effectiveness of topiramate and other drugs for migraine prevention (Appendix Table D70). Most trials did not report funding source or conflict of interest (Appendix Table D71). All trials but one were double blind with low or medium risk of bias (Appendix Table D72).

Individual RCTs provided low-strength evidence that topiramate was more effective than amitriptyline in reducing monthly headache days by ≥50 percent with no differences in monthly migraine days (Table 13).[189] Topiramate was more effective than lamotrigine in reducing monthly headache intensity by ≥50 percent.[99] Differences were small (less than 20 percent absolute risk difference) but statistically significant (Appendix Table D73). Decrease in headache frequency by ≥50 percent did not differ between topiramate and zonasamide,[190] valproate,[191] levetiracetam,[192] or lamotrigine.[99] Topiramate was more effective than propranolol in reducing absolute migraine frequency, duration, and intensity.[193]

Beta Blockers for Episodic Migraine

Propranolol

Most RCTs that examined the comparative effectiveness of propranolol for migraine prevention in adults (Appendix Table D74) failed to report funding (Appendix Table D75). Most trials were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D76). Few trials met pooling criteria (Table 14).

Propranolol Versus Topiramate

The likelihood of ≥50 percent reduction in monthly migraine frequency did not differ between topiramate and propranolol (Table 13 and Appendix Table D35).[105] Topiramate was more effective than propranolol in reducing absolute migraine frequency, duration, and intensity.[193] Use of drugs for acute attacks did not differ between the two drugs.[105]

Propranolol Versus Timolol

The likelihood of ≥50 percent reduction in monthly migraine frequency did not differ between propranolol and timolol (Table 14).[104,107]

Propranolol Versus Metoprolol

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 (Table 14).[194,195]

Propranolol Versus Nifedipine

Propranolol was more effective than nifedipine in reducing monthly migraine frequency by ≥50 percent (Table 14).[195,196]

Propranolol Versus Clonidine

The likelihood of ≥50 percent reduction in migraine days did not differ between propranolol and clonidine (Table 13).[197]

Propranolol Versus Nadolol

Nadolol, 160 mg/day, was more effective than propranolol in achieving a reduction of ≥50 percent in migraine frequency, duration, and intensity (Table 13).[198] Differences between a lower dose of nadolol (80 mg/day) and propranolol (160 mg/day) were not significant.[198,199]

Propranolol Versus Antidepressants

The likelihood of ≥50 percent reduction in monthly migraine attacks did not differ between propranolol and amitriptyline[200] nortriptyline,[188] or femoxetine.[201] 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.[188]

Off-Label Drugs

Off-Label Beta Blockers

RCTs that examined comparative effectiveness of off-label beta blockers for migraine prevention in adults (Appendix Table D77) failed to report funding and conflict of interest (Appendix Table D78). All trials were double blind (Appendix Table D79). All RCTs examined unique drug comparisons except two RCTs that compared the effects of metoprolol and aspirin.

Metoprolol Versus Aspirin

In pooled analyses, metoprolol and aspirin resulted in similar rates of ≥50 percent reduction in monthly migraine attacks (Table 14).[202,203] Individual RCTs reported that metoprolol was more effective than aspirin, 300 mg/day,[202] but less effective than aspirin, 1,500 mg/day.[203]

Metoprolol Versus Nifedipine

Metoprolol was more effective than nifedipine in reducing monthly migraine attacks by ≥50 percent (Table 13).[195]

Metoprolol Versus Bisoprolol (Appendix Table D80)

Metoprolol and bisoprolol did not differ for reduction in monthly migraine attacks by ≥50 percent nor absolute number of migraine days (Appendix Table D81).[204,205]

Metoprolol Versus Nebivolol (Evidence Table D80)

Reduction in monthly migraine attacks by ≥50 percent did not differ between metoprolol and nebivolol.[206] Neither migraine-related disability, use of drugs for acute attacks (Appendix Table D82), nor quality of life (Appendix Table D80) differed between metoprolol and nebivolol.[206]

Metoprolol Versus Clonidine

Reduction in monthly migraine attacks by ≥50 percent did not differ between metoprolol and clonidine.[207] However, more patients noticed a reduction in migraine days with metoprolol than clonidine (Appendix Table D82).[207]

Antidepressants

Individual RCTs found no differences in the comparative effectiveness of antidepressants for migraine prevention. The likelihood of reducing monthly migraine attacks by ≥50 percent did not differ between femoxetine and propranolol, nor did the duration or intensity of attacks or use of acute drugs differ.[201] Fluoxetine combined with amitriptyline versus amitriptyline alone resulted in similar migraine frequency and severity.[208] Fluvoxamine versus amitriptyline resulted in similar migraine frequency and severity.[209] Venlafaxine versus amitriptyline resulted in similar migraine frequency and severity.[210]

Indirect Evidence of Comparative Effectiveness of Preventive Drugs for Episodic Migraine

Among all included RCTs, 97 percent examined the outcome of clinically important reduction in migraine frequency by ≥50 percent. We found no consistent differences in baseline patient characteristics in RCTs that examined the efficacy of various drugs for migraine prevention. We conducted exploratory Bayesian network meta-analysis (Appendix Table D83) and indirect adjusted analysis of such drugs (Appendix Table D84). We found no differences among approved drugs (Table 15). Approved drugs were more effective than off-label drugs except for the angiotensin II receptor blocker candesartan, which was more effective than topiramate, divalproex, and propranolol (Table 16). Exploratory Bayesian network meta-analysis demonstrated that the approved drugs topiramate, divalproex, and propranolol, and off-label drug classes except ergot alkaloids were better than placebo (Figure 3). The strength of the association was the largest with angiotensin inhibiting drugs (Table 17).

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 angiotensin inhibiting drugs were more effective than all other treatments. 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.

Table 13. Comparative effectiveness of approved and off-label drugs on migraine prevention (50% or more reduction) in adults with episodic migraine, results from individual head-to-head randomized controlled clinical trials

Active vs. Control Drug Weeks From Randomization to Time to Measure Outcome	Reference	Sample	% With Outcome With Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Topiramate vs. Amitriptyline 26 weeks	Dodick, 2009[189]	347	55.6 [45.9]	1.2 (1.0 to 1.5)	0.09 (-0.01 to 0.20)	NS	NS	Low	Yes	NA	Imprecise	Low
Topiramate vs. Lamotrigine 20 weeks	Gupta, 2007[99]	120	63.0 [46.0]	1.4 (1.0 to 1.9)	0.17 (-0.01 to 0.34)	NS	NS	Low	Yes	NA	Imprecise	Low
Topiramate vs. Propranolol 26 weeks	Diener, 2004[105]	288	34.7 [43.1]	0.8 (0.6 to 1.1)	-0.08 (-0.20 to 0.03)	NS	NS	Low	Yes	NA	Imprecise	Low
Topiramate vs. Levetiracetam 8 weeks	de Tommaso, 2007[192]	28	61.5 [53.3]	1.2 (0.6 to 2.2)	0.08 (-0.28 to 0.45)	NS	NS	Medium	Yes	NA	Imprecise	Low
Propranolol vs. Clonidine 16 weeks	Kass, 1980[197]	46	56.5 [34.8]	1.6 (0.8 to 3.2)	0.22 (-0.06 to 0.50)	NS	NS	Medium	Yes	NA	Imprecise	Low
Propranolol vs. Femoxetine 12 weeks	Kangasniemi, 1983[201]	29	20.0 [7.1]	2.8 (0.3 to 23.9)	0.13 (-0.11 to 0.37)	NS	NS	Medium	Yes	NA	Imprecise	Low
Propranolol vs. Nadolol 12 weeks	**Sudilovsky, 1987[211]**	**91**	**11.4 [38.3]**	**0.3 (0.1 to 0.7)**	**-0.27 (-0.44 to -0.10)**	**-4 (2 to 10)**	**-269 (102 to 437)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Femoxetine vs. Propranolol 12 weeks	Kangasniemi, 1983[201]	24	27.3 [7.7]	3.5 (0.4 to 29.4)	0.20 (-0.10 to 0.50)	NS	NS	Medium	Yes	NA	Imprecise	Low
Nortriptyline vs. Propranolol 8 weeks	Domingues, 2009[188]	49	29.2 [44.0]	0.7 (0.3 to 1.4)	-0.15 (-0.41 to 0.12)	NS	NS	Medium	Yes	NA	Imprecise	Low
Metoprolol vs. Bisoprolol 12 weeks	Worz, 1992[205]	250	8.8 [9.6]	0.9 (0.4 to 2.0)	-0.01 (-0.08 to 0.06)	NS	NS	Medium	Yes	NA	Imprecise	Low
Metoprolol vs. Nebivolol 18 weeks	Schellenberg, 2008[206]	30	57.0 [50.0]	1.1 (0.6 to 2.2)	0.07 (-0.29 to 0.43)	NS	NS	Medium	Yes	NA	Imprecise	Low

Table 13. Comparative effectiveness of approved and off-label drugs on migraine prevention (50% or more reduction) in adults with episodic migraine, results from individual head-to-head randomized controlled clinical trials (continued)

Active vs. Control Drug Weeks From Randomization to Time to Measure Outcome	Reference	Sample	% With Outcome With Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Risk of Bias	Direct	Consistency	Precision	Strength of Evidence
Metoprolol vs. Nifedipine 28 weeks	**Gerber, 1991[195]**	**39**	**27.3 [0.0]**	**10.2 (0.6 to 168.9)**	**0.27 (0.07 to 0.47)**	**4 (2 to 14)**	**273 (74 to 472)**	**Medium**	**Yes**	**NA**	**Imprecise**	**Low**
Metoprolol vs. Clonidine 8 weeks	Louis, 1985[207]	62	32.3 [25.8]	1.3 (0.6 to 2.7)	0.06 (-0.16 to 0.29)	NS	NS	Medium	Yes	NA	Imprecise	Low
Nadolol vs. Propranolol 24 weeks	Olerud, 1986[199]	28	38.5 [60.0]	0.6 (0.3 to 1.4)	-0.22 (-0.58 to 0.15)	NS	NS	Medium	Yes	NA	Imprecise	Low
Lisuride vs. Methysergide 12 weeks	Hermann, 1977[212]	253	53.1 [51.2]	1. 0(0.8 to 1.3)	0.02 (-0.10 to 0.14)	NS	NS	Medium	Yes	NA	Imprecise	Low

CI = confidence interval; NA = not applicable; NS= not significant

Number needed to treat and number of attributable events were calculated for statistically significant differences.

Bold = significant differences when 95% CI of absolute risk difference do not include 0.

Table 14. Comparative effectiveness of drugs for migraine prevention in adults with episodic migraine, direct evidence from head-to-head randomized controlled clinical trials (pooled with random effects model)

Active Preventive Treatment References	Outcome	Sample	Rate, Percent With Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence Reasons for Lowering SOE
Timolol vs. Propranolol[104,107]	≥50% decrease in migraine frequency	242	47.9 [52.1]	1.0 (0.7 to 1.2)	-0.03(-0.15 to 0.10)	NS	NS	Low (medium ROB, imprecision)
	p value			0.593	0.606			
	I squared			0	0			
Propranolol vs. Metoprolol[194,195]	≥50% decrease in migraine frequency	113	38.2 [50.0]	0.8 (0.5 to 1.2)	-0.12 (-0.30 to 0.06)	NS	NS	Low (medium ROB, imprecision)
	p value			p = 0.371	p = 0.361			
	I squared			0	0			
Propranolol vs. Nifedipine[195,196]	≥50% decrease in migraine frequency	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)
Metoprolol vs. Aspirin[202,203]	≥50% decrease in migraine frequency	326	33.1 [39.3]	1.6 (0.2 to 11.0)	0.11 (-0.43 to 0.65)	NS	NS	Low (medium ROB, imprecision)
	p value			0.001	0			
	I squared			0.907	0.948			

ROB = risk of bias; SOE = strength of evidence; NS= not significant; CI = confidence interval

Bold = significant effects of drugs on treatment response when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences

Table 15. Indirect adjusted comparative effectiveness of clinical response* in RCTs of approved drugs for the prophylaxis of episodic migraine

Active	Control -- Propranolol	Control -- Timolol	Control -- Topiramate	Control -- Divalproex
Divalproex	1.1 (0.4 to 2.9)	1.0 (0.4 to 2.7)	0.9 (0.3 to 2.5)	1
Propranolol	1	0.9 (0.4 to 1.7)	0.8 (0.4 to 1.6)	0.9(0.3;2.3)
Timolol	1.2(0.6;2.3)	1	1.0 (0.5 to 2.0)	1.0(0.4;2.9)
Valproate	1.4 (0.5 to 4.5)	1.2 (0.4 to 4.1)	1.2 (0.4 to 3.8)	1.3 (0.3 to 5.0)

CI = confidence interval; RCT = randomized controlled trial

*Clinical response was defined as ≥50 percent reduction in monthly migraine frequency or self-reported substantial reduction in monthly migraine frequency Differences are significant when 95% CI of odds ratios do not include 1; odds ratios of each drug versus placebo were compared with each other to calculate presented odds ratios with 95% CI.

Table 16. Indirect adjusted comparative effectiveness of clinical response* in RCTs of approved drugs versus off-label drugs for the prophylaxis of episodic migraine

Active	Control -- Divalproex	Control Propranolol	Control -- Timolol	Control -- Topiramate	Control -- Valproate
Acebutolol	2.8 (0.5;16.7)	3.2 (0.6;15.9)	2.7 (0.5;14.2)	2.6 (0.5;13.5)	2.2 (0.3;14.5)
Acetazolamide	0.3 (0.1;1.2)	0.3 (0.1;1.1)	0.3 (0.1;1.0)	**0.3 (0.1;0.9)**	0.2 (0.0;1.1)
Amitriptyline	1.0 (0.3;3.9)	1.1 (0.4;3.5)	1.0 (0.3;3.2)	0.9 (0.3;3.0)	0.8 (0.2;3.5)
Aspirin	**0.3 (0.1;0.6)**	**0.3 (0.2;0.4)**	**0.2 (0.1;0.4)**	**0.2 (0.1;0.4)**	**0.2 (0.1;0.6)**
Atenolol	8.0 (0.4;167.6)	9.0 (0.5;171.2)	7.7 (0.4;150.9)	7.5 (0.4;144.4)	6.3 (0.3;139.7)
Candesartan	**5.7 (1.0;32.2)**	**6.4 (1.4;30.4)**	**5.5 (1.1;27.3)**	**5.3 (1.1;26.0)**	4.5 (0.7;28.1)
Clonidine	0.7 (0.2;2.4)	0.8 (0.3;2.0)	0.7 (0.3;1.9)	0.7 (0.2;1.8)	0.6 (0.1;2.1)
Dihydroergotamine	0.4 (0.1;1.0)	**0.4 (0.2;0.8)**	**0.4 (0.2;0.7)**	**0.4 (0.2;0.7)**	**0.3 (0.1;0.9)**
Fenoprofen	**0.2 (0.1;0.9)**	**0.3 (0.1;0.8)**	**0.2 (0.1;0.8)**	**0.2 (0.1;0.7)**	**0.2 (0.0;0.8)**
Flurbiprofen	1.7 (0.4;7.6)	1.9 (0.5;7.0)	1.6 (0.4;6.3)	1.5 (0.4;6.0)	1.3 (0.3;6.7)
Indomethacin	0.4 (0.1;2.1)	0.5 (0.1;2.0)	0.4 (0.1;1.8)	0.4 (0.1;1.7)	0.3 (0.1;1.9)
Lamotrigine	0.6 (0.2;1.7)	0.6 (0.3;1.4)	0.5 (0.2;1.3)	0.5 (0.2;1.3)	0.4 (0.1;1.6)
Lisinopril	11.9 (0.6;233.2)	13.4 (0.8;237.7)	11.6 (0.6;209.6)	11.2 (0.6;200.5)	9.4 (0.4;194.7)
Lisuride	0.6 (0.2;1.7)	0.6 (0.3;1.4)	0.5 (0.2;1.3)	0.5 (0.2;1.2)	0.4 (0.1;1.5)
Montelukast	0.4 (0.1;1.2)	0.4 (0.2;1.0)	**0.4 (0.2;0.9)**	**0.4 (0.2;0.8)**	0.3 (0.1;1.1)
Nadolol	1.9 (0.1;42.4)	2.1 (0.1;43.4)	1.8 (0.1;38.2)	1.8 (0.1;36.6)	1.5 (0.1;35.3)
Nifedipine	3.2 (0.7;14.2)	3.6 (1.0;13.0)	3.1 (0.8;11.8)	3.0 (0.8;11.2)	2.5 (0.5;12.6)
Oxcarbazepine	**0.3 (0.1;0.8)**	Not able to calculate	**0.3 (0.1;0.6)**	**0.3 (0.1;0.6)**	**0.2 (0.1;0.7)**
Rofecoxib	0.8 (0.2;2.9)	**0.3 (0.1;0.6)**	0.8 (0.3;2.3)	0.8 (0.3;2.2)	0.7 (0.2;2.6)
Telmisartan	0.5 (0.1;1.8)	0.6 (0.2;1.6)	0.5 (0.2;1.4)	0.5 (0.2;1.4)	0.4 (0.1;1.6)
Tolfenamic Acid	3.8 (0.6;23.2)	4.2 (0.8;22.1)	3.7 (0.7;19.8)	3.5 (0.7;18.8)	3.0 (0.4;20.1)
Tonabersat	0.4 (0.1;1.1)	0.4 (0.2;1.0)	**0.4 (0.1;0.9)**	**0.3 (0.1;0.8)**	0.3 (0.1;1.0)
Gabapentin	0.8 (0.3;2.5)	0.9 (0.4;1.8)	0.7 (0.3;1.7)	0.7 (0.3;1.6)	.59 (0.2;2.0)
Mg	0.5 (0.1;1.7)	0.5 (0.2;1.3)	0.4 (0.2;1.2)	0.4 (0.2;1.2)	0.4 (0.1;1.4)
Nimodipine	2.0 (0.2;0.0)	2.1 (0.2;24.3)	1.8 (0.2;21.6)	1.8 (0.2;20.6)	1.42 (0.1;0.0)

CI = confidence interval; RCT = randomized controlled trial

*Clinical response was defined as ≥50 percent reduction in monthly migraine frequency or self-reported substantial reduction in monthly migraine frequency Bold = differences are significant when 95% CI of odds ratios do not include 1; odds ratios of each drug vs. placebo were compared with each other to calculate presented odds ratios with 95% CI

Table 17. Odds ratio of clinical response with preventive drugs, results from exploratory Bayesian network meta-analysis

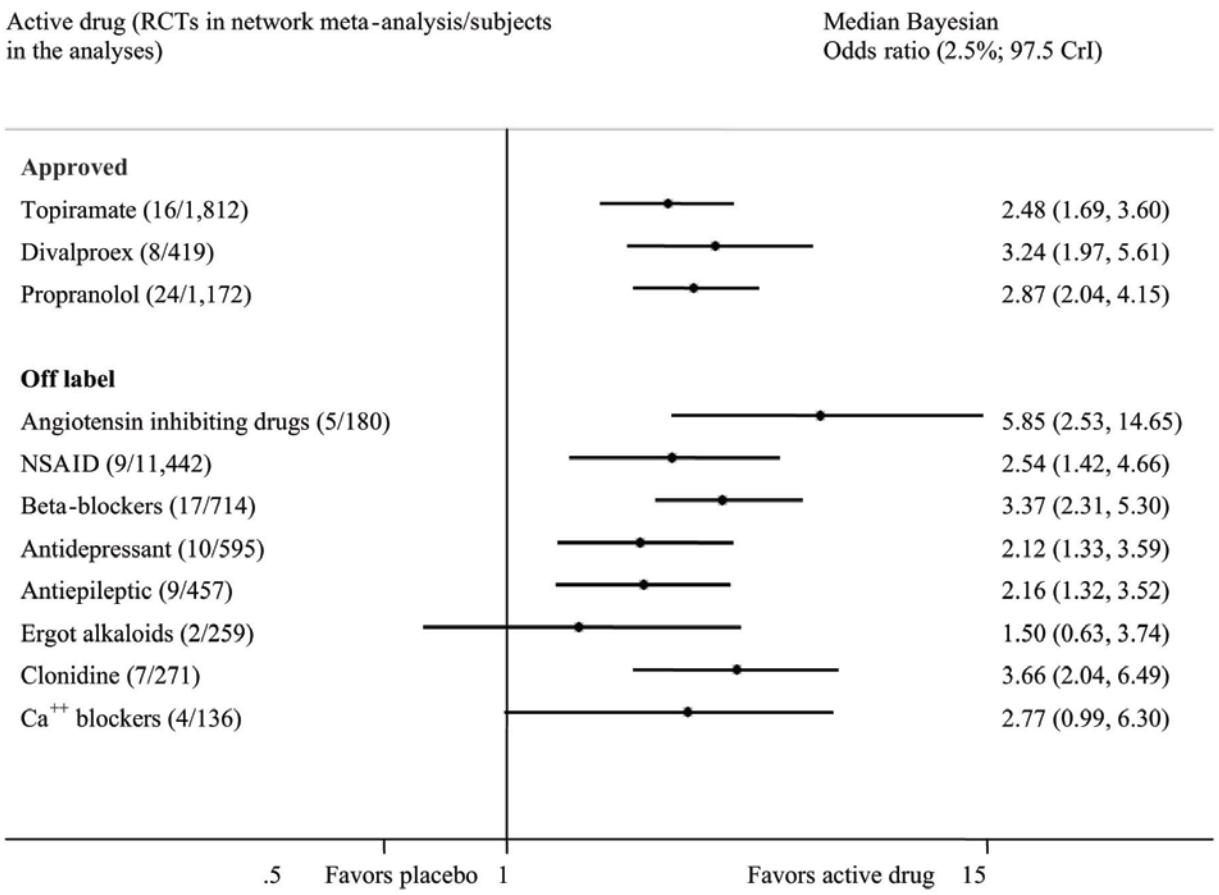
Active	Subjects	Control -- Divalproex	Control -- Propranolol	Control -- Angiotensin Inhibiting Drugs	Control -- NSAiD	Control -- Beta Blockers	Control -- Antidepressants	Control -- Antiepileptics	Control -- Ergot Alkaloids	Control -- Clonidine	Control -- Ca ++ Blockers
Topiramate 16 RCTs	1,812	0.8 (0.4 to 1.4)	0.9 (0.5 to 1.4)	0.4 (0.2 to 1.1)	1.0 (0.5 to 1.9)	0.7 (0.4 to 1.2)	1.2 (0.6 to 2.0)	1.2 (0.7 to 2.0)	1.7 (0.6 to 4.2)	0.7 (0.3 to 1.3)	0.9 (0.4 to 2.7)
Divalproex 8 RCTs	419	1	1.1 (0.6 to 2.0)	0.6 (0.2 to 1.6)	1.3 (0.6 to 2.8)	1.0 (0.5 to 1.9)	1.5 (0.7 to 3.1)	1.5 (0.8 to 3.1)	2.2 (0.8 to 5.9)	0.9 (0.4 to 1.9)	1.2 (0.5 to 3.6)
Propranolol 24 RCTs	1,172	0.9 (0.5 to 1.5)	1	0.5 (0.2 to 1.2)	1.1 (0.6 to 2.2)	0.8 (0.5 to 1.3)	1.3 (0.8 to 2.3)	1.3 (0.8 to 2.4)	1.9 (0.7 to 4.8)	0.8 (0.4 to 1.4)	1.0 (0.4 to 2.9)
Angiotensin inhibiting drugs 5 RCTs	180	1.8 (0.6 to 5.2)	2.1 (0.8 to 5.2)	1	2.3 (0.8 to 6.6)	1.7 (0.7 to 4.6)	2.8 (1.0 to 7.5)	2.7 (1.0 to 7.5)	3.9 (1.2 to 13.8)	1.6 (0.6 to 4.5)	2.1 (0.7 to 8.2)
NSAID 9 RCTs	11,442	0.8 (0.4 to 1.7)	0.9 (0.5 to 1.7)	0.4 (0.2 to 1.2)	1	0.7 (0.4 to 1.4)	1.2 (0.6 to 2.5)	1.2 (0.6 to 2.6)	1.7 (0.6 to 4.6)	0.7 (0.3 to 1.6)	0.9 (0.3 to 2.9)
Beta blockers 17 RCTs	714	1.0 (0.5 to 2.0)	1.2 (0.7 to 1.9)	0.6 (0.2 to 1.5)	1.3 (0.7 to 2.6)	1	1.6 (0.9 to 2.9)	1.6 (0.9 to 3.1)	2.3 (0.9 to 5.9)	0.9 (0.5 to 1.7)	1.2 (0.5 to 3.6)
Antidepressants 10 RCTs	595	0.7 (0.3 to 1.4)	0.7 (0.4 to 1.3)	0.4 (0.1 to 1.0)	0.8 (0.4 to 1.8)	0.6 (0.3 to 1.2)	1	1.0 (0.5 to 2.0)	1.4 (0.5 to 3.8)	0.6 (0.3 to 1.2)	0.8 (0.3 to 2.3)
Antiepileptics 9 RCTs	457	0.7 (0.3 to 1.3)	0.8 (0.4 to 1.3)	0.4 (0.1 to 1.0)	0.9 (0.4 to 1.8)	0.6 (0.3 to 1.2)	1.0 (0.5 to 2.0)	1	1.4 (0.5 to 3.9)	0.6 (0.3 to 1.3)	0.8 (0.3 to 2.3)
Ergot alkaloids 2 RCTs	259	0.5 (0.2 to 1.3)	0.5 (0.2 to 1.4)	0.3 (0.1 to 0.9)	0.6 (0.2 to 1.7)	0.4 (0.2 to 1.2)	0.7 (0.3 to 1.9)	0.7 (0.3 to 2.0)	1	0.4 (0.1 to 1.2)	0.5 (0.2 to 2.1)
Clonidine 7 RCTs	271	1.1 (0.5 to 2.4)	1.3 (0.7 to 2.3)	0.6 (0.2 to 1.7)	1.4 (0.6 to 3.2)	1.1 (0.6 to 2.0)	1.7 (0.8 to 3.6)	1.7 (0.8 to 3.7)	2.4 (0.8 to 6.7)	1	1.3 (0.5 to 4.1)
Ca++ blockers 4 RCTs	136	0.9 (0.3 to 2.2)	1.0 (0.4 to 2.3)	0.5 (0.1 to 1.5)	1.1 (0.3 to 2.9)	0.8 (0.3 to 2.0)	1.3 (0.4 to 3.2)	1.3 (0.4 to 3.4)	1.8 (0.5 to 6.0)	0.8 (0.2 to 2.1)	1

NSAID = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial

*Clinical response (defined as ≥50 percent reduction in monthly episodic migraine frequency or self-reported substantial reduction in monthly migraine frequency Bold = differences are significant when 2.5 to 97.5% credible intervals of odds ratios do not include 1.

We used heterogeneous random effects model that assumes correlation within study (rho = 0.5) and heterogeneous between studies (WinBUG codes are in Appendix B) NSAID nonsteroidal anti-inflammatory drugs.

Figure 3. Bayesian network meta-analysis of clinical response to drugs versus placebo (66 RCTs of 14,774 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults



CrI = credible intervals; NSAID = nonsteroidal anti-inflammatory drugs
Clinical response was defined as ≥50% reduction in monthly migraine attacks or perceived clinically important treatment success. We used heterogeneous random effects model that assumes correlation within study (rho = 0.5) and heterogeneous between studies (WinBUG codes are in Appendix B).

KQ1c. How do preventive pharmacologic treatments affect patient-centered and intermediate outcomes when compared with active nonpharmacologic treatments?

Antiepileptics

Topiramate Versus Exercise or Relaxation

The likelihood of ≥50 percent reduction in monthly migraine frequency did not differ between topiramate and aerobic exercise or common forms of relaxation, breathing, and stress-management techniques.[213] Migraine days, pain intensity, quality of life, or acute drug use did not differ between topiramate and aerobic exercise or relaxation.[213]

Beta Blockers

Propranolol Versus Biofeedback

The likelihood of a reduction in monthly migraine frequency of ≥25 percent did not differ between propranolol and diaphragmatic breathing and systematic relaxation that was assisted by biofeedback and also practiced at home.[214]

Antidepressants

Amitriptyline Versus Spinal Manipulation

Amitriptyline was more effective than spinal manipulation for reducing monthly migraine attacks during the trial but less effective during post-treatment followup period.[215] Evidence was low-strength due to risk of bias and imprecision (Appendix Table D85). Evidence from a single high-risk-of-bias RCT was insufficient to conclude the comparative effectiveness of amitriptyline versus biofeedback.[216]

KQ1d. How do preventive pharmacologic treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared with pharmacologic treatments alone?

Five RCTs compared the effectiveness of drugs combined with nondrug treatments with placebo or pharmacologic treatments alone (Appendix Table D86). Most trials were funded by nonprofit grants (Appendix Table D87). Risk of bias was low in one trial, medium in two, and high in two (Appendix Table D88).

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 D89). However, effects of the combined therapy did not differ from the effects of drugs alone.[217] Evidence of effectiveness and safety was low due to imprecise estimates from a single RCT (Appendix Table D90).[217] We estimated that 387 adults per 1,000 treated would experience a reduction in migraine frequency by ≥50 percent (95% CI, 157 to 618) with combined therapy (Table 18).[217]

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, reducing impact of migraines, stress management or biofeedback training, and migraine management plan) was more effective than placebo in improving self-efficacy (Appendix Table D91).[218]

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.[216]

Antidepressants

Amitriptyline Combined With Spinal Manipulation Versus Amitriptyline Alone or Spinal Manipulation Alone (Table 19)[215]

Spinal manipulation was more effective than combined treatment in reducing Headache Index scores.[215] Combined treatment was not more effective than amitriptyline alone in improving general health status or reducing use of drugs for acute attacks (Appendix Table D92).[215] Evidence from a single high-risk-of-bias RCT was insufficient to conclude comparative effectiveness between amitriptyline combined with biofeedback and the drug alone.[216]

Table 18. Comparative effectiveness of beta blockers combined with behavioral therapy* for episodic migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[217]

Outcome	Active Treatment	Control	Sample	Rate % in Active [Control] Group	Number Needed To Treat (95% CI)	Attributable Events (95% CI)	Strength of Evidence
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 (2 to 4)**	**-423 (262 to 583)**	**Low**

CI = confidence interval; NS= not significant

*Behavioral therapy included 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; Bold = significant at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0. Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 19. Comparative effectiveness of antidepressant amitriptyline and spinal manipulation for episodic migraine prevention in adults, individual medium risk of bias randomized controlled clinical trial[215]

Definition of the Outcome	Active Treatment	Control Treatment	Sample	Rate, % With Active vs. [Control] Treatment	Number Needed To Treat (95% CI)	Attributable Events per 1,000 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**

CI = confidence interval; HI = Headache Index; NS = not significant

Number needed to treat and number of attributable events were calculated for statistically significant differences.

Bold = significant differences at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.

KQ1e1. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

Muscle Relaxants

Onabotulinumtoxin A

Dose Response Migraine Prevention With Onabotulinumtoxin A

Higher doses of onabotulinumtoxin A resulted in a greater decrease in absolute migraine frequency according to the BoNTA-024-026-036 Study Group in adults with chronic migraine.[219] Higher doses of onabotulinumtoxin A 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 D93).[138] However, neither patients nor investigators found differences in global assessment of improvement with higher doses of onabotulinumtoxin A (Appendix Table D94).[139]

Higher doses of abobotulinumtoxin A did not increase the rates of positive global assessment of the treatment effect in the Dysport® In Migraine Without Aura Prophylaxis trial.[139] Higher doses of abobotulinumtoxin A did not reduce migraine duration or intensity[139] or depression scores.[144]

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 D95). Higher topiramate doses (50 to 100 mg) resulted in significant migraine prevention of ≥50 percent in one patient for every six treated (Table 20).

Divalproex

Higher doses of divalproex did not result in a greater likelihood of clinically important migraine frequency reduction (Appendix Table D96).[103]

Beta Blockers

Propranolol

Increasing propranolol dose did not result in a greater likelihood of clinically important reduction in migraine frequency.[220-223]

Off-Label Beta Blockers

Individual RCTs examined dose response effects with pindolol,[224] nadolol,[225,226] and bisoprolol.[227]

Pindolol

Pindolol, 15 mg/day, was more effective than 7.5 mg in reducing migraine days and duration.[224]

Nadolol

Nadolol, 160 to 240 mg/day, was more effective than 80 mg/day in reducing migraine frequency and severity.[225,226]

Bisoprolol

Bisoprolol, 10 mg/day, was more effective than 5 mg/day in reducing migraine duration but not frequency.[227]

Antidepressants

Amitriptyline

Amitriptyline, 50 mg/day, was not more effective than 25 mg/day in reducing migraine frequency or severity.[228]

Venlafaxine

Venlafaxine, 150 mg/day, resulted in excellent global self-reported efficacy more often than 75 mg/day.[165]

Table 20. Dose response reduction in migraine attacks by ≥50% from baseline with topiramate in adults

Reference Risk of Bias	Topiramate Daily Doses	Events/Randomized With Larger vs. Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events (95% CI)
Brandes, 2004[229] 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)	NS	NS
Silberstein, 2003[97] Risk of bias: Medium	**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[230] 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	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[229] 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)	NS	NS
Silberstein, 2003[97] Risk of bias: Medium	**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[230] 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	**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[229] 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)	NS	NS
Silberstein, 2003[97] Risk of bias: Medium	200mg/day vs. 100mg/day	58/112 68/125	1.0 (0.8 to 1.2)	-0.02 (-0.15 to 0.11)	NS	NS
Silberstein, 2004[230] 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)	NS	NS
Pooled	200mg/day vs. 100mg/day	176/350 196/375	1.0 (0.8 to 1.1)	-0.02 (-0.09 to 0.05)	NS	NS

CI = confidence interval; NS = not significant

Bold = significant at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.

Number needed to treat and number of attributable events were calculated for statistically significant differences.

KQ1e2. 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 the effectiveness of drug management for migraine prevention in adults (Table 21 and Appendix Table D97). Most trials were sponsored by nonprofit organizations (Appendix Table D98). Half of the trials had low risk of bias, and the other half had medium risk of bias due to inadequacy of randomization (Appendix Table D99). Four RCTs examined the effectiveness of multidisciplinary migraine management programs and two examined the effectiveness of pharmacist-led drug management (Appendix Table D100).

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 group lectures with a dietitian[231] (Appendix Table D100). Adherence did not differ between the multidisciplinary intervention and standard medical care with the patient's primary physician (Appendix Table D101).[231] The multidisciplinary intervention was more effective in improving quality of life and reducing migraine-related disability (Appendix Table D102).[231] We found no statistically significant changes in medication use or work status.[231]

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.[232] The program included an educational session in which patients received materials that described: migraine types and etiologies, triggers, sleep hygiene, pharmacologic treatment, and relaxation techniques.[232] 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 D103).[232] We estimated that 196 adults per 1,000 treated (95% CI, 125 to 258) would have no migraine-related disability with the migraine management intervention.[232] The program was also more effective than usual care in improving quality of life and treatment satisfaction (Appendix Table D104).[232]

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.[233] The cognitive-behavioral minimal contact program did not decrease migraine frequency or duration of migraine related disability (Appendix Table D105),[233] nor did it improve engagement in social activity, self-management of pain, migraine-related anxiety, or depression.[233] However, patient satisfaction with treatment was significantly greater with the cognitive-behavioral minimal contact program than with usual care.[233]

Headache School Versus Usual Care

Headache school involved a standardized curriculum of didactic instructions regarding migraine biogenesis and management. It 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.[234] Patients in the control group received routine drug management.[234] Patients who attended headache school less often overused drugs for acute attacks than patients receiving routine drug management (Appendix Table D106).[234] Attending headache school also reduced migraine disability (Appendix Table D107).[234]

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.[235] Patients in the control group received standard counseling that included general information about benefits and possible adverse drug effects.[235] Pharmaceutical care resulted in a statistically significant improvement from baseline in mental health and self-efficacy.[236] However, the likelihood of complete migraine cessation did not differ between active and control interventions (Appendix Table D108)[235] nor did the absolute number of migraine attacks or quality of life (Appendix Table D109).[235]

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.[236] 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.[236] The campaign had no statistically significant impact on use of triptans (Appendix Table D110).[236]

Table 21. 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[231] Multidisciplinary intervention vs. standard medical care with the patient's family physician Sample: 80 Risk of bias: Medium	Multidisciplinary intervention 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[232] Headache management program vs. continue with current clinician Sample: 614 Risk of bias: Medium	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 U.S. Headache Consortium guidelines); and (3) proactive followup by a case-manager.	More effective in improving quality of life and satisfaction with care; 196 adults per 1,000 treated (95% CI, 125 to 258) had no migraine-related disability with the headache management program.
Fritsche, 2010[233] Cognitive-behavioral minimal contact program (MCT) vs. two brochures Sample: 158 Risk of bias: Low	The program consisted of 5 sessions with six participants and lasting 2 hours each: (1) Introduction and syndrome education; (2) Medication rules and the risk of medication overuse headache, including information about prophylactic migraine medication and medication overuse; (3) Medication intake behavior, aimed at raising awareness for "external" and "internal" influences on patient's medication intake behavior; (4) General and personal risk factors for drug intake; and (5) Everyday transfer aimed at 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[234] Standardized course of didactic instructions regarding migraine biogenesis and management ("headache school") Sample: 100 Risk of bias: Medium	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 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[235] 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[236] 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.

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

We identified 15 RCTs and six nonrandomized studies that examined the safety of onabotulinumtoxin A for chronic migraine prevention in adults. We identified 159 RCTs of 18,134 adults that examined the safety of drugs for episodic migraine prevention in adults.

Among approved drugs, onabotulinumtoxin A, topiramate, and propranolol resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.

The association was dose responsive for topiramate. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.

Individual RCTs showed that divalproex caused adverse effects that led to treatment discontinuation, including nausea, somnolence, tremor, vomiting, and asthenia.

Among other drugs, pooled analyses demonstrated that off-label antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo.

Limited low-strength direct comparative evidence from individual head-to-head RCTs suggested that treatment discontinuation due to adverse effects was less frequent with onabotulinumtoxin A than topiramate or amitriptyline. Individual unique RCTs provided low-strength direct evidence about adverse effects with specific drugs with no consistent pattern across available drug comparisons.

Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analyses demonstrated that topiramate and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. According to network meta-analysis, off-label angiotensin inhibiting drugs and beta blockers were the safest treatment option for adults with episodic migraine.

KQ2a. What are the harms from preventive pharmacologic treatments when compared with placebo or no active treatment?

We identified 83 RCTs that compared adverse drug effects with placebo. Most studies failed to disclose conflict of interest by trial investigators (Appendix Table D111). The results from these 83 trials that were a subset of RCTs that examined benefits with drugs for episodic migraine prevention in adults were applicable to the target population (Appendix Table D112). Women made up an average of 78 percent of all enrollees. Mean age of the enrollees varied from 29 to 49 years. Patients had an average 5.5 monthly migraine attacks. The trials followed for an average 18 weeks to assess adverse effects (Appendix Table D113). Sample size averaged 116 adults (range 12 to 818). RCTs reporting harms were not necessarily powered to detect statistically significant differences in adverse effects.

We concluded medium risk of bias in 54 RCTs and low risk of bias in 22 RCTs (Appendix Table D114). Most studies were double blind. Nonrandomized studies with high risk of bias suggested that 10 to 20 percent of patients discontinued antiepileptic drug treatments at one year or longer of followup (Appendix Table D115).

We focused on treatment discontinuation due to any and specific adverse effects from pooled analyses (Table 22).

Muscle Relaxants

Onabotulinumtoxin A

Fifteen RCTs examined the safety of botulinum toxin for chronic migraine prevention in adults including 13 RCTs of onabotulinumtoxin A and two RCTs of abobotulinumtoxin A (Appendix Table D8). Onabotulinumtoxin A resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo (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 23). The results were robust and remained significant with different methods of pooling (Appendix Tables D116 and D117). Abobotulinumtoxin A RCTs did not report treatment discontinuation due to adverse effects.[139,144]

Among individual adverse effects, neck pain and muscle weakness were the most common (Table 23). Increase in risk of adverse effects with onabotulinumtoxin A was lower in trials with higher placebo rates of adverse effects (Table 24). Increase in risk of adverse effects was dose responsive (Appendix Table D118). Patients experienced eyelid edema with 50U of onabotulinumtoxin A more often than with 25U.[219] Higher doses of 150 to 225U of onabotulinumtoxin A resulted in greater risk of blepharoptosis, muscle weakness, and neck rigidity (Appendix Table D118).

Abobotulinumtoxin A

Abobotulinumtoxin A RCTs reported increased risk of neck weakness in 109 patients per 1,000 treated (95% CI, 22 to 196).[139,144] The rates of the total adverse effects were statistically higher with the increased dose of the drug (210U versus 80U).[144] The rates of specific adverse effects did not differ between the active drug and placebo.[139,144]

Antiepileptics

Topiramate

Most RCTs that examined safety with topiramate versus placebo for episodic migraine prevention in adults (Appendix Table D119) were funded by industry and reported conflict of interest by principal investigators (Appendix Table D120). All trials were double blind (Appendix Table D121).

Patients stopped taking topiramate more often than placebo because of intolerable adverse effects including fatigue, paresthesia, and taste perversion (Table 25). 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 D122). Compared with placebo, topiramate more often resulted in bothersome taste perversion, paresthesia, and fatigue leading to withdrawal (Appendix Table D123).

Pooled estimates were consistent with imprecision that decreased strength of evidence. 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. Published pooled analysis of individual patient data demonstrated topiramate discontinuation due to anorexia, anxiety, depression, hypoesthesia, and nausea (Appendix Table D124).[237] Some adverse effects leading to treatment discontinuation were reported in individual RCTs that failed to show statistically significant increase in risk of specific harms with topiramate (Appendix Table D125).

Topiramate increased risk of specific adverse effects. Individual RCTs reported small numbers of events. Pooled analyses demonstrated a statistically significant increase in risk of any adverse effect, paresthesia, cognitive difficulties, diarrhea, dry mouth, fatigue, nausea, taste alteration or perversion, and weight loss (Appendix Table D126). Topiramate caused adverse effects in one patient for every eight treated. Taste alteration, weight loss, and paresthesia were the most common adverse effects (Table 26). Individual RCTs reported increased risk of severe anorexia and mood problems (Table D127).

Risk of adverse effects was dose responsive according to the published pooled analyses of individual patient data (Appendix Table D128).[237] Larger doses of topiramate increased risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal.[237] Larger doses of topiramate increased risk of dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.[237]

Divalproex

Adverse effects with divalproex versus placebo were examined in three RCTs that examined efficacy of divalproex for episodic migraine prevention in adults (Appendix Table D25). All three RCTs were funded by industry (Appendix Table D26) and all were double blind (Appendix Table D27).

Treatment discontinuation due to adverse effects did not differ with divalproex versus placebo (Table 22 and Appendix Table D122).[101,102] 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. Larger doses of divalproex did not increase risk of bothersome adverse effects leading to treatment discontinuation (Appendix Table D129).[103] Larger doses of divalproex increased risk of nausea and tremor (Appendix Table D130).[103]

Valproate

Adverse effects of valproate were examined in two small double-blind RCTs of 75 adults that examined efficacy of valproate for episodic migraine prevention in adults (Appendix Tables D25-D27).

Treatment discontinuation due to adverse effects did not differ with valproate versus placebo (Table 22).[153] Rates of combined adverse effects did not differ between valproate and placebo (Appendix Table D131).[120,153]

Beta Blockers

Propranolol

All RCTs that examined safety with propranolol versus placebo in adults with episodic migraine (Appendix Table D31) were double blind but did not analyze the data according to planned intention-to-treat principles (Appendix Table D33). Propranolol increased risk of bothersome adverse effects leading to treatment discontinuation more often than placebo (Table 22).[106,238]

Propranolol resulted in adverse effects more often than placebo (Appendix Table D132). Among individual adverse effects, propranolol more often than placebo resulted in diarrhea (pooled 89 attributable events per 1,000 treated; 95% CI, 14 to 164) and nausea (pooled 43 attributable events per 1,000 treated 95% CI, 9 to 77).

Timolol

Treatment discontinuation due to bothersome adverse effects did not differ with timolol and placebo in adults with episodic migraine (low-strength evidence from individual RCT) (Table 28). Timolol increased risk of overall adverse effects but not of any specific examined adverse effects more often than placebo (Appendix Tables D133 and D134).

Off-Label Drugs

Antiepileptics

All RCTs that examined the safety of six off-label antiepileptic drugs for episodic migraine, including acetazolamide, gabapentin, vigabatrin, oxcarbazepine, carbamazepin, and lamotrigine (Appendix Table D39) were double blind (Appendix Table D41). Pooled analyses demonstrated no differences in treatment discontinuation due to adverse effects with gabapentin or lamotrigine versus placebo (Table 22 and Appendix Table D135) but increase in risk of the total adverse effects with gabapentin (Appendix Table D136). Antiepileptic drugs increased risk of the specific adverse effects as follows.

Acetazolamide

Acetazolamide caused paresthesia, drowsiness, memory impairment, malaise, and fasciculation more often than placebo in adults with episodic migraine (Appendix Table D137).[117]

Carbamazepin

Carbamazepin caused adverse effects that led to dose reductions more often than placebo in adults with episodic migraine. Specific adverse effects included vertigo and drowsiness. (Appendix Table D138).[118]

Gabapentin

Gabapentin caused somnolence and dizziness more often than placebo in adults with episodic migraine (Appendix Table D139)[111]; however, the validity of the results was questioned due to exclusion of patients from the analyses and biased tolerability conclusions.[239]

Lamotrigine

Treatment discontinuation due to the specific side effects, including rash, occurred more frequently with lamotrigine than placebo in adults with episodic migraine (Appendix Table D140).[240] A fixed dose of 200 mg/day of lamotrigine caused skin rash more often than placebo. In contrast, a gradually escalated dose of lamotrigine starting with 25 mg/day did not cause skin rash.[240]

Oxcarbazepine

Oxcarbazepine caused adverse effects including fatigue, dizziness, and nausea more often than placebo in adults with episodic migraine (Appendix Table D141).[119]

Antidepressants

Pooled analyses demonstrated that amitriptyline but not femoxetine caused adverse effects leading to treatment discontinuation more often than placebo in adults with episodic migraine (Table 22). Amitriptyline increased the risk of dizziness, drowsiness, and constipation (Appendix

Table D142). Femoxetine and fluoxetine increased the risk of any adverse effects (Appendix Table D142).

Cortical Spreading Depression Inhibitor

Individual RCTs demonstrated no differences between placebo and tonabersat in treatment discontinuation due to bothersome adverse effects in adults with episodic migraine.[127]

Beta Blockers

Atenolol

Treatment discontinuation due to bothersome adverse effects did not differ between atenolol and placebo in adults with episodic migraine (Appendix Table D143).[123,159,241] Less than 1 percent of participants discontinued atenolol due to bothersome side effects (Appendix Table D144).[123,159,241] Among all examined adverse effects, only rates of slight orthostatic dizziness during the first week of treatments were greater with atenolol than with placebo.

Bisoprolol

Treatment discontinuation due to bothersome adverse effects did not differ between bisoprolol and placebo in adults with episodic migraine.[227] In fact, side effects occurred no more often from bisoprolol than from placebo (Appendix Table D144). A higher dose of bisoprolol did not result in greater rates of adverse effects or treatment discontinuation due to adverse effects.[227] Bisoprolol, 10 mg/day, decreased heart rate when compared with 5 mg/day.[227] Systolic and diastolic blood pressure did not differ with two doses of bisoprolol.[227]

Metoprolol

Treatment discontinuation due to bothersome adverse effects did not differ between metoprolol and placebo in adults with episodic migraine.[114] Rates of total adverse effects were greater with metoprolol than with placebo in a single RCT.[113] Metoprolol caused fatigue and sleep disturbances more often than placebo (Appendix Table D145).[113]

Nadolol

Treatment discontinuation due to bothersome adverse effects did not differ between nadolol and placebo in adults with episodic migraine.[124] In fact, nadolol caused adverse effects no more often than placebo. An increased dose of nadolol did not result in greater rates of adverse effects.[225,226]

Pindolol

Treatment discontinuation due to bothersome adverse effects did not differ with pindolol and placebo in adults with episodic migraine.[160] Patients experienced orthostatic dizziness and faintness more often with pindolol than with placebo.[160]

Ergot Alkaloids

In individual underpowered RCTs, treatment discontinuation due to bothersome adverse effects did not differ with placebo, lisuride, or methysergide in adults with episodic migraine.[131,242]

Angiotensin Converting Enzyme Inhibitors

Individual RCTs of adults with episodic migraine did not examine treatment discontinuation to bothersome adverse effects with lisinopril[128] or captopril.[88] Captopril caused adverse effects no more often than placebo.[88] The rates of any adverse effects were greater with lisinopril than placebo; 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.[128]

Angiotensin II Antagonists

Individual RCTs did not examine treatment discontinuation to bothersome adverse effects with candesartan[129] or telmisartan in adults with episodic migraine.[173] Neither drug caused any adverse effect more often than placebo.[129,173]

Calcium Channel Antagonists

Treatment discontinuation due to bothersome adverse effects did not differ between placebo and nifedipine,[243] nimodipine,[112,244] or verapamil in adults with episodic migraine.[171]

Compared with placebo, verapamil more often caused tolerable constipation that did not result in treatment discontinuation.[171] Nifedipine resulted in adverse effects more often than placebo.[243] Among individual adverse effects, nifedipine increased rates of headache, dizziness, and edema.[243] Nimodipine increased rates of abdominal cramps but no other examined adverse effects.[89]

NSAID

Individual RCTs found no differences in bothersome adverse effects leading to treatment discontinuation with fenoprofen,[245] naproxen sodium,[246] or tolfenamic acid in adults with episodic migraine.[134] Among individual adverse effects, fenoprofen increased rates of fatigue and somnolence.[245]

KQ2b. What are the harms from preventive pharmacologic treatments when compared with active pharmacologic treatments?

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

Muscle Relaxants

Onabotulinumtoxin A for Chronic Migraine

Comparative safety of onabotulinumtoxin A versus topiramate was examined in two RCTs that demonstrated better safety with onabotulinumtoxin A than topiramate (Appendix Table D146).[183,186] Patients experienced depression or mood disturbance, weight loss, paresthesias, or cognitive deficits more often with topiramate (Appendix Table D146).[183,186]

A single RCT examined the comparative safety of onabotulinumtoxin A versus divalproex sodium and found a higher risk of ptosis with onabotulinumtoxin A (Appendix Table D147).[184] In contrast, risk of fatigue, nausea, and total adverse effects was higher with divalproex (Appendix Table D147).

A single RCT examined the comparative safety of onabotulinumtoxin A versus amitriptyline and concluded better safety with onabotulinumtoxin A (Appendix Table D148).[185] Patients

experienced dry mouth, constipation, somnolence, and weight gain several times more often with amitriptyline than with onabotulinumtoxin A.[185]

Topiramate

Treatment discontinuation due to adverse effects did not differ between topiramate and amitriptyline in adults with episodic migraine (Table 22).[189,247] Comparative safety of topiramate with other drugs was examined in individual RCTs. Treatment discontinuation due to any adverse effects did not differ between topiramate and zonasamide or valproate (Table 29). Treatment discontinuation due to specific adverse effects differed with topiramate and other drugs according to individual RCTs (Appendix Table D149). Somnolence or weight increase leading to withdrawal was less common with topiramate than amitriptyline (Table 29).[189,247] Treatment discontinuation to treatment failure, however, did not differ between topiramate and amitriptyline or lamotrigine (Appendix Table D150).

Risk of specific adverse effects differed between topiramate and other drugs in individual RCTs in adults with episodic migraine (Appendix Table D151). Topiramate increased risk of weight loss when compared with amitriptyline,[189] levetiracetam,[192] and valproate[248] (Appendix Table D151). Topiramate increased risk of paresthesia when compared with amitriptyline[189,247] (Appendix Table D151). Risk of dry mouth and constipation was lower with topiramate than amitriptyline (Appendix Table D152).[189,247] Individual RCTs demonstrated higher risk of headache with topiramate than amitriptyline (Appendix Table D153).

Comparative safety of topiramate combined with amitriptyline versus monotherapy was examined in one small RCT.[247] Treatment discontinuation due to adverse effects did not differ between topiramate combined with amitriptyline and monotherapy.[247] The risk of adverse effects was lower with combined therapy when compared with amitriptyline alone but not topiramate alone (Appendix Table D154).[247]

Beta Blockers for Episodic Migraine

Propranolol

Treatment discontinuation due to bothersome adverse effects did not differ between propranolol and aspirin (Table 28).[249] Evidence of comparative safety with propranolol ergotamine intake was insufficient due to high risk of bias in individual RCT (Appendix Table D155).

Treatment discontinuation due to adverse effects did not differ between behavioral migraine management and propranolol (Appendix Table D156).[217] Treatment discontinuation due to bothersome adverse effects did not differ between combined behavioral migraine management with propranolol versus propranolol alone.[217] Combined therapy was more effective than propranolol alone in having self-efficacy and internal control over headache (Appendix Table D157).[218]

Off-Label Drugs for Episodic Migraine

Off-Label Beta Blockers

Metoprolol Versus Clonidine

Metoprolol resulted in treatment discontinuation due to bothersome adverse effects or treatment failure less often than clonidine (Table 30 and Appendix Table D158).[207]

Metoprolol Versus Bisoprolol

Treatment discontinuation due to adverse effects did not differ between the two drugs (Table 30 and Appendix Table D158)[204] nor did rates of individual examined adverse effects differ between the drugs (Appendix Table D159).

Metoprolol Versus Nebivolol

Treatment discontinuation due to adverse effects did not differ between the two drugs (Table 30).[206] Patients experienced moderate adverse effects, fatigue, and bradycarida more often with metoprolol than with nebivolol (Appendix Table D159).[206]

Metoprolol Versus Aspirin

Gastrointestinal side effects leading to withdrawal were more common with aspirin than metoprolol (Table 30 and Appendix Table D158).[202] However, autonomic nervous system and psychiatric disorders were more common with metoprolol than aspirin (Appendix Table D159).[203]

Metoprolol Versus Clomipramine

Treatment discontinuation because of severe adverse reactions was more common with clomipramine than metoprolol (Table 30).[250] Clomipramine caused insomnia and sweating more often than metoprolol (Appendix Table D159).[250]

Antidepressants

Clomipramine Versus Metoprolol

Clomipramine resulted in treatment discontinuation due to bothersome adverse effects more often than metoprolol (Table 30).[250]

Femoxetine Versus Propranolol

Treatment discontinuation due to bothersome adverse effects did not differ between femoxetine and propranolol.[201]

Amitriptyline Versus Spinal Manipulation

Treatment discontinuation due to adverse effects occurred less with spinal stimulation than with amitriptyline (Table 31).[215] Strength of evidence was low due to risk of bias and imprecise estimate (Appendix Table D160).[215]

Treatment discontinuation due to adverse effects did not differ between combined treatment using spinal manipulation with amitriptyline and amitriptyline alone (Appendix Table D161).[215]

Ergot Alkaloids

A single RCT of 253 adults (low-strength evidence) found that treatment discontinuation due to adverse effects was less common with lisuride than with methysergide.[212]

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

Bothersome adverse effects leading to treatment discontinuation were examined in 68 RCTs. Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs (Appendix Table D162). Exploratory Bayesian network meta-analyses demonstrated that topiramate, off-label antiepileptics, and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Figure 4). According to network meta-analysis, off-label angiotensin inhibiting drugs and beta blockers were the safest treatment option for adults with episodic migraine (Appendix Table D163)

KQ2c. 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. Treatment discontinuation due to adverse effects with migraine preventive drugs in adults, evidence from meta-analyzed randomized controlled clinical trials

Active Preventive Treatment	Sample	Rate, Percent With Drug [Control]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence Reasons for Lowering SOE
Compared With Placebo							
Chronic Migraine							
Onabotulinumtoxin A[137,251]	**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 (medium ROB)**
Episodic Migraine							
Topiramate[27,85,96, 99,146,148,150,252]	**2055**	**16.6 [8.5]**	**1.8 (1.3 to 2.4)**	**0.06 (0.02 to 0.11)**	**16(9 to 53)**	**63(19 to 107)**	**Low (medium ROB, Imprecise)**
Divalproex[101,102]	346	9.8 [7.8]	1.2 (0.5 to 2.7)	0.02 (-0.05 to 0.10)	NS	NS	Low (medium ROB, Imprecise , Inconsistent)
Valproate[120,153]	150	6.7 [5.3]	1.3 (0.3 to 4.9)	0.01 (-0.07 to 0.08)	NS	NS	Low (medium ROB, Imprecise)
Propranolol[106,238]	**221**	**13.2 [5.6]**	**2.1 (0.6 to 7.7)**	**0.06 (0.00 to 0.12)**	**16 (8 to 333)**	**62 (3 to 120)**	**Low (medium ROB, Imprecise, Inconsistent)**
Gabapentin[87,110,111]	270	17.0 [7.7]	1.9 (0.9 to 4.2)	0.07 (-0.01 to 0.15)	NS	NS	Low (medium ROB, Imprecise)
Lamotrigine[99,240]	178	12.8 [6.0]	2.4 (0.5 to 12.2)	0.14 (-0.17 to 0.44)	NS	NS	Low (Imprecise , Inconsistent)
Amitriptyline[125,253]	**507**	**11.2 [5.8]**	**1.9 (1.0 to 3.5)**	**0.05 (0.01 to 0.10)**	**19 (10 to 167)**	**54 (6 to 102)**	**Low (medium ROB, Imprecise)**
Femoxetine[167,168]	124	11.7 [6.3]	1.9 (0.6 to 6.1)	0.05 (-0.05 to 0.15)	NS	NS	Low (medium ROB, Imprecise)
Clonidine[177,254]	334	2.4 [0.6]	2.8 (0.4 to 18.5)	0.02 (-0.01 to 0.05)	NS	NS	Low (medium ROB, Imprecise)
Nimodipine[112,244]	155	3.9 [6.3]	0.7 (0.2 to 2.6)	-0.03 (-0.09 to 0.04)	NS	NS	Low (medium ROB, Imprecise , Inconsistent)
Naproxen[246,255]	172	3.5 [1.2]	2.3 (0.3 to 15.4)	0.02 (-0.03 to 0.07)	NS	NS	Low (High ROB, Imprecise , Inconsistent)
Magnesium[115,116]	150	7.7 [1.4]	3.8 (0.7 to 22.4)	0.06 (0.00 to 0.13)	NS	NS	Low (Inconsistent Imprecise)

Table 22. Treatment discontinuation due to adverse effects with migraine preventive drugs in adults, evidence from meta-analyzed randomized controlled clinical trials (continued)

Active Preventive Treatment	Sample	Rate, Percent With Drug [Control]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence Reasons for Lowering SOE
Compared With Active Treatment, Episodic Migraine							
Topiramate vs. amitriptyline[189,247]	399	18.3 [21.3]	0.9 (0.6 to 1.3)	-0.04 (-0.11 to 0.04)	NS	NS	Low (medium ROB, imprecision)

CI = confidence interval; ROB = risk of bias; SOE = strength of evidence; NS = not significant
Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 23. Adverse effect with onabotulinumtoxin A versus placebo for chronic migraine prevention in adults (magnitude of the effect and strength of evidence from randomized controlled clinical trials)

Adverse Effect	Sample, References	Rate, Percent With Onabotulinumtoxin A [Placebo]	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence
Any adverse effect	**5031[94,137,138,142,144,219,251,256,257]**	**47.5 [29.4]**	**6 (5 to 11)**	**155 (90 to 220)**	**Moderate**
Back pain	**1112[93,138,257]**	**2.2 [0.5]**	**59 (32 to 333)**	**17 (3 to 31)**	**High**
Discontinuations related to adverse effect	**1384[137,251]**	**3.8 [1.1]**	**38 (23 to 100)**	**26 (10 to 43)**	**Moderate**
Dizziness	893[93,94,139,257]	1.7 [0.9]	NS	NS	Moderate
Dysphagia	**1057[94,138]**	**3.3 [0.3]**	**36 (23 to 83)**	**28 (12 to 44)**	**High**
Eyelid edema	915[139,219,257]	3.6 [0.3]	NS	NS	High
Headache	2204[94,138,139,219,256,257]	5.2 [4.5]	NS	NS	High
Hypertonia	**1426[94,138,257]**	**7.1 [1.3]**	**16 (12 to 24)**	**62 (42 to 82)**	**High**
Neck pain	**2233[94,139,251,257]**	**14.1 [1.4]**	**9 (6 to 17)**	**111 (58 to 164)**	**Moderate**
Neck rigidity	**1467[93,94,138,257]**	**9.2 [1.8]**	**13 (9 to 24)**	**75 (41 to 110)**	**Moderate**
Pain	2319[93,94,138,139,257]	3.6 [2.1]	NS	NS	Moderate
Blepharoptosis	**2454[92,94,138,139,144,219,256,257]**	**6.4 [0.8]**	**20 (14 to 34)**	**49 (29 to 69)**	**High**
Muscle weakness	**1968[94,138,251,256]**	**15.8 [0.1]**	**8 (5 to 18)**	**132 (56 to 209)**	**Moderate**
Fever	587[93,139,219]	5.3 [7.1]	NS	NS	Moderate

CI = confidence interval; NS = not significant
Bold = Differences were significant when 95% CI of attributable events per 1,000 treated do not include 0.
Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 24. Adverse effects with onabotulinumtoxin A versus placebo in adults with chronic migraine, 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 of 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 of 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 of 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

CI = confidence interval|

Bold = significant differences at 95% confidence limit when 95% CI do not include 0.

Table 25. Treatment discontinuation due to adverse effects with topiramate versus placebo in adults, pooled with random effects results from randomized controlled clinical trials

Reason for Treatment Discontinuation References	Sample	Rate with Topiramate [Placebo]	Pooled Relative Risk (95% CI)	Pooled Absolute Risk Difference (95% CI)	Number Needed To Treat To Harm (95% CI)	Attributable Events per 1,000 Treated (95% CI)
Cognitive difficulties[27,96,252]	939	7.3 [2.0]	2.8 (0.5 to 15.3)	0.05 (-0.02 to 0.12)	NS	NS
Difficulty with memory[237,252]	765	1.7 [1.1]	1.2 (0.1 to 16.3)	0.01 (-0.01 to 0.03)	NS	NS
Dizziness[27,252]	824	1.9 [2.0]	0.7 (0.1 to 5.1)	-0.02 (-0.11 to 0.07)	NS	NS
Fatigue[27, 105,252]	**824**	**4.5 [0.9]**	**2.8 (0.4 to 21.2)**	**0.04 (0.01 to 0.06)**	**28 (17 to 71)**	**36 (14 to 58)**
Insomnia[27,252]	824	3.1 [1.2]	1.3 (0.1 to 15.1)	0.01 (-0.04 to 0.06)	NS	NS
Language problems[237,252]	766	2.2 [0.4]	3.7 (0.7 to 20.3)	0.02 (0.00 to 0.03)	NS	15 (0 to 31)
Paresthesia[27,96,252]	939	8.4 [0.7]	9.6 (3.5 to 26.5)	0.08 (0.05 to 0.10)	13 (10 to 20)	75 (49 to 101)
Somnolence[96,237]	831	2.1 [1.8]	1.1 (0.4 to 3.2)	0.00 (-0.02 to 0.02)	NS	NS
Taste perversion[96,237,252]	**881**	**1.5 [0.0]**	**3.8 (0.7 to 21.4)**	**0.01 (0.00 to 0.02)**	**77 (42 to 1000)**	**13 (1 to 24)**

CI = confidence interval; NS = not significant

Bold = significant differences when 95% CI of absolute risk difference do not include 0.

Number needed to treat and number of attributable events were calculated for statistically significant differences.

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

Outcome, Reference	Sample	Rate With Topiramate [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed To Treat To Harm (95% CI)	Attributable Events per 1,000 Treated (95% CI)
Adverse events[85,99,100,146,148,237]	**1700**	**59.9 [56.1]**	**1.2 (1.0 to 1.3)**	**0.12 (0.02 to 0.22)**	**8 (4 to 42)**	**124 (24 to 223)**
Paresthesia[85,95,96,98-100,146,148,237,252]	**1876**	**24.0 [5.5]**	**4. 7(3.4 to 6.3)**	**0.24 (0.14 to 0.33)**	**4 (3 to 7)**	**235 (142 to 328)**
Weight decrease[85,95,96,149,237,252]	**1648**	**12.3 [4.4]**	**3.6 (1.5 to 8.3)**	**0.10 (0.05 to 0.15)**	**10 (6 to 19)**	**104 (53 to 154)**
Cognitive difficulties[96,100,105,146,149,237,52]	**1782**	**8[3]**	**2.2 (1.1 to 4.4)**	**0.045 (0.01 to 0.08)**	**22(13 to 100)**	**45 (10 to 80)**
Diarrhea[148,150,237]	**1170**	**9.8 [3.6]**	**2.7 (1.5 to 4.7)**	**0.06 (0.01 to 0.10)**	**18 (10 to 71)**	**57 (14 to 100)**
Dry mouth[86,148,237]	**1429**	**6.1 [2.7]**	**2.5 (1.4 to 4.3)**	**0.04 (0.01 to 0.06)**	**29 (18 to 71)**	**35 (14 to 57)**
Fatigue[100,237]	**1857**	**9.6 [4.6]**	**1.7 (1.3 to 2.3)**	**0.05 (0.03 to 0.08)**	**20 (13 to 38)**	**50 (26 to 75)**
Hyperesthesia[146,148,237]	**1756**	**7.4 [1.6]**	**3.5 (1.8 to 6.5)**	**0.06 (0.03 to 0.08)**	**18 (13 to 30)**	**57 (33 to 80)**
Insomnia[84,105,150,252]	878	4 [2]	1.6 (0.5 to 4.7)	0.02 (0.001 to 0.04)	NS	21 (1 to 42)
Memory impairment[85,86,100,105,150,237,252]	**1436**	**10.4 [3.9]**	**2.4 (1.2 to 4.6)**	**0.058 (0.017 to 0.099)**	**17 (10 to 59)**	**58 (17 to 99)**
Nausea[85,105,146,148,149,237]	**2156**	**11[6]**	**1.5 (1.1 to 2.0)**	**0.034 (0.003 to 0.065)**	**29 (15 to 333)**	**34 (3 to 65)**
Taste perversion[86,95,96,105,148,237,252]	**1634**	**5.9 [1.3]**	**4.9 (2.5 to 9.8)**	**0.083 (0.025 to 0.14)**	**12 (7 to 40)**	**83 (25 to 140)**
Abdominal pain[149,237]	1229	2.0 [2.3]	0.9 (0.4 to 2.0)	0.00 (-0.02 to 0.02)	NS	NS
Anorexia[85,95,99,100,146,148,149,237,252]	2424	5.6 [3.3]	1.8 (1.2 to 2.7)	0.03 (0.00 to 0.05)	NS	NS
Back pain[148,237]	1100	4.6 [5.1]	0.9 (0.5 to 1.6)	0.00 (-0.03 to 0.02)	NS	NS
Giddiness[85,99,100,146,148,237,252]	1871	10.1 [7.8]	1.2 (0.8 to 1.7)	0.01 (-0.02 to 0.04)	NS	NS
Dyspepsia[100,237]	1018	1.5 [1.1]	1.3 (0.4 to 3.8)	0.01 (-0.03 to 0.05)	NS	NS
Infection, viral[100,148]	444	8.2 [8.0]	1.0 (0.6 to 1.9)	0.00 (-0.05 to 0.05)	NS	NS
Injury[146,148,237]	1672	5.0 [6.1]	0.8 (0.2 to 3.2)	-0.01 (-0.07 to 0.04)	NS	NS
Adverse events: Serious[86,149]	842	7.9 [6.6]	1.1 (0.6 to 2.1)	0.01 (-0.05 to 0.06)	NS	NS
Sinusitis[146,148,237]	1429	7.4 [6.4]	1.1 (0.7 to 1.7)	0.01 (-0.02 to 0.03)	NS	NS
Sleepiness[85,86,96,98,100,148,237,252]	1893	4.4 [3.4]	1.5 (0.8 to 3.0)	0.02 (-0.01 to 0.04)	NS	NS
Language problems[150,237,252]	657	3.6 [0.5]	4.8 (1.1 to 20.5)	0.09 (-0.03 to 0.21)	NS	NS
Upper respiratory tract infection[85,86,148,237]	1641	8.7 [9.0]	1.0 (0.7 to 1.4)	0.00 (-0.03 to 0.03)	NS	NS
Vision, abnormal[95,237]	756	7.7 [2.2]	3.3 (1.4 to 7.8)	0.07 (-0.01 to 0.15)	NS	NS

CI = confidence interval; NS = not significant

Number needed to treat and number of attributable events were calculated for statistically significant differences.

Bold = significant differences when 95% CI of absolute risk difference do not include 0.

Table 27. Treatment discontinuation due to bothersome adverse effects and adverse effects with divalproex versus placebo for episodic 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 1,000 Treated (95% CI)	Strength of Evidence
Discontinuations due to intolerance	Mean average dose 1087 mg/d	Mathew, 1995[101]	107	12.9 [5.4]	NS	NS	
Discontinuations due to intolerance	Mean average dose 871 mg/d	Freitag, 2002[102]	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[102]	239	6.5 [5.2]	NS	NS	Low
Alopecia	**Mean average dose 1087 mg/d**	**Mathew, 1995[101]**	**107**	**12.9 [0.0]**	**8 (5 to 24)**	**129 (41 to 216)**	**Low**
Any	Mean average dose 871 mg/d	Freitag, 2002[102]	239	67.5 [69.8]	NS	NS	Low
Asthenia	**Mean average dose 1087 mg/d**	**Mathew, 1995[101]**	**107**	**31.4 [8.1]**	**4 (3 to 11)**	**233 (93 to 373)**	**Low**
Asthenia	500 mg	Klapper, 1997[103]	60	8.9 [9.1]	NS	NS	Low
Asthenia	1000 mg	Klapper, 1997[103]	57	9.3 [9.1]	NS	NS	Low
Asthenia	1500 mg	Klapper, 1997[103]	58	22.7 [9.3]	NS	NS	Low
Asthenia	Mean average dose 871 mg/d	Freitag, 2002[102]	239	7.3 [10.3]	NS	NS	Low
Back pain	500 mg	Klapper, 1997[103]	60	6.7 [9.1]	NS	NS	Low
Back pain	1000 mg	Klapper, 1997[103]	57	4.7 [9.1]	NS	NS	Low
Back pain	1500 mg	Klapper, 1997[103]	58	13.6 [9.3]	NS	NS	Low
Diarrhea	500 mg	Klapper, 1997[103]	60	6.7 [4.5]	NS	NS	Low
Diarrhea	1000 mg	Klapper, 1997[103]	58	4.7 [4.5]	NS	NS	Low
Diarrhea	1500 mg	Klapper, 1997[103]	59	18.2 [4.6]	NS	NS	Low
Diarrhea	Mean average dose 871 mg/d	Freitag, 2002[102]	239	7.3 [3.4]	NS	NS	Low
Dizziness	500 mg	Klapper, 1997[103]	60	6.7 [4.5]	NS	NS	Low
Dizziness	1000 mg	Klapper, 1997[103]	58	7.0 [4.5]	NS	NS	Low
Dizziness	1500 mg	Klapper, 1997[103]	59	20.5 [4.6]	NS	NS	Low
Dyspepsia	500 mg	Klapper, 1997[103]	60	6.7 [9.1]	NS	NS	Low
Dyspepsia	1000 mg	Klapper, 1997[103]	57	18.6 [9.1]	NS	NS	Low
Dyspepsia	1500 mg	Klapper, 1997[103]	58	15.9 [9.3]	NS	NS	Low
Dyspepsia	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	6.5 [4.3]	NS	NS	Low
Flu syndrome	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	8.1 [8.6]	NS	NS	Low
Infection	500 mg	Klapper, 1997[103]	60	17.8 [18.2]	NS	NS	Low
Infection	1000 mg	Klapper, 1997[103]	58	16.3 [18.2]	NS	NS	Low
Infection	1500 mg	Klapper, 1997[103]	59	20.5 [18.6]	NS	NS	Low

Table 27. Treatment discontinuation due to bothersome adverse effects and adverse effects with divalproex versus placebo for episodic 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 1,000 Treated (95% CI)	Strength of Evidence
Infection	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	14.6 [13.8]	NS	NS	Low
Nausea	**Mean average dose of divalproex sodium was 1087 mg/d**	**Mathew, 1995[101]**	**107**	**45.7 [13.5]**	**3 (2 to 6)**	**322 (162 to 482)**	**Low**
Nausea	**500 mg**	**Klapper, 1997[103]**	**60**	**26.7 [6.8]**	**5 (3 to 52)**	**200 (19 to 381)**	**Low**
Nausea	1000 mg	Klapper, 1997[103]	57	9.3 [6.8]	NS	NS	Low
Nausea	**1500 mg**	**Klapper, 1997[103]**	**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[102]	239	14.6 [8.6]	NS	NS	Low
Pain	500 mg	Klapper, 1997[103]	60	8.9 [6.8]	NS	NS	Low
Pain	1000 mg	Klapper, 1997[103]	57	7.0 [6.8]	NS	NS	Low
Pain	1500 mg	Klapper, 1997[103]	59	11.4 [7.0]	NS	NS	Low
Sinusitis	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	3.3 [7.8]	NS	NS	Low
Somnolence	**Mean average dose 1087 mg/d**	**Mathew, 1995[101]**	**107**	**30.0 [5.4]**	**4 (3 to 9)**	**246 (116 to 376)**	**Low**
Somnolence	500 mg	Klapper, 1997[103]	60	6.7 [4.5]	NS	NS	Low
Somnolence	1000 mg	Klapper, 1997[103]	58	7.0 [4.5]	NS	NS	Low
Somnolence	1500 mg	Klapper, 1997[103]	59	18.2 [4.6]	NS	NS	Low
Somnolence	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	6.5 [1.7]	NS	NS	Low
Tremor	**Mean average dose 1087 mg/d**	**Mathew, 1995[101]**	**107**	**12.9 [0.0]**	**8 (5 to 24)**	**129 (41 to 216)**	**Low**
Tremor	500 mg	Klapper, 1997[103]	60	0.0 [0.0]	NS	NS	Low
Tremor	1000 mg	Klapper, 1997[103]	57	7.0 [0.0]	NS	NS	Low
Tremor	**1500 mg**	**Mathew, 1995[101]**	**59**	**15.9 [0.0]**	**6 (3 to 48)**	**159 (21 to 297)**	**Low**
Vomiting	**Mean average dose 1087 mg/d**	**Mathew, 1995[101]**	**107**	**18.6 [0.0]**	**5 (4 to 11)**	**186 (88 to 284)**	**Low**
Vomiting	500 mg	Klapper, 1997[103]	60	4.4 [2.3]	NS	NS	Low
Vomiting	1000 mg	Klapper, 1997[103]	57	4.7 [2.3]	NS	NS	Low
Vomiting	1500 mg	Klapper, 1997[103]	58	11.4 [2.3]	NS	NS	Low
Vomiting	Mean average dose of study: 871 mg/d	Freitag, 2002[102]	239	6.5 [1.7]	NS	NS	Low

CI = confidence interval; NS = not significant

Bold = significant difference at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.

Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 28. Treatment discontinuation due to adverse effects with propranolol or timolol for episodic 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 effects	Propranolol	Aspirin	Baldrati, 1983[249]	36	11.1	16.7	NS	NS	Low
Moderate chest pain on day 28 leading to discontinuation	Timolol	Placebo	Stellar, 1984[109]	94	2.1	0	NS	NS	Low
Discontinued therapy because of severe epigastric distress and fecal impaction	Timolol	Placebo	Stellar, 1984[109]	94	2.1	0	NS	NS	Low
Withdrew due to adverse experiences	Timolol	Placebo	Stellar, 1984[109]	94	4.3	0	NS	NS	Low

CI = Confidence interval; NS = not significant

Bold = significant at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.

Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 29. Treatment discontinuation due to any adverse effects with topiramate versus other drugs for episodic 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 1,000 Treated (95% CI)	Strength of Evidence
Aggravation of migraine leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	0.0 [1.8]	NS	NS	Low
Anxiety leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	1.7 [0.0]	NS	NS	Low
Confusion leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	1.7 [0.0]	NS	NS	Low
Dizziness leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	1.7 [0.0]	NS	NS	Low
Dry mouth leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	0.0 [1.8]	NS	NS	Low
Fatigue leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	3.4 [2.4]	NS	NS	Low
Hypoesthesia leading to withdrawal	Topiramate	Amitriptyline	Dodick, 2009[189]	347	1.7 [0.0]			Low
Somnolence leading to withdrawal	**Topiramate**	**Amitriptyline**	**Dodick, 2009[189]**	**347**	**0.0 [4.1]**	**-24 (14 to 104)**	**-41 (10 to 73)**	**Low**
Weight increase leading to withdrawal	**Topiramate**	**Amitriptyline**	**Dodick, 2009[189]**	**347**	**0.0 [4.7]**	**-21 (12 to 73)**	**-47 (14 to 81)**	**Low**
Withdrew due to drowsiness	Topiramate	Valproate (slow-release)	Bartolini, 2005[191]	44	9.1 [13.6]	NS	NS	Low
Left the study due to impaired concentration	Topiramate	Zonasamide	Mohammadiani nejad, 2011[190]	80	0.0 [2.5]	NS	NS	Low
Left the study due to intolerable paresthesia	Topiramate	Zonasamide	Mohammadiani nejad, 2011[190]	80	5.0 [0.0]	NS	NS	Low
Left the study due to unbearable restless leg syndrome	Topiramate	Zonasamide	Mohammadiani nejad, 2011[190]	80	0.0 [2.5]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 100mg	Amitriptyline 100mg	Dodick, 2009[189]	347	19.7 [22.5]	NS	NS	Low
Discontinued due to adverse effects	Topiramate + Amitriptyline amitriptyline	Amitriptyline	Keskinbora, 2008[247]	51	4.3 [14.3]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 200mg	Amitriptyline 150mg	Keskinbora, 2008[247]	52	8.3 [14.3]	NS	NS	Low

Table 29. Treatment discontinuation due to any adverse effects with topiramate versus other drugs for episodic migraine prevention in adults (continued)

Adverse Effects Leading to Withdrawal	Active	Control	Reference	Sample	Rate, Percent With Topiramate [Control Drug]	Number Needed To Treat (95% CI)	Attributable Events per 1,000 Treated (95% CI)	Strength of Evidence
Discontinued due to adverse effects	Topiramate 200mg)	Topiramate + Amitriptyline	Keskinbora, 2008[247]	47	8.3 [4.3]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[99]	120	5.0 [5.0]	NS	NS	Low
Discontinued due to adverse effects	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[192]	28	7.7 [0.0]	NS	NS	Low

CI = confidence interval; NS = not significant
Bold = significant at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.
Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 30. Comparative safety of beta blockers for episodic 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 1,000 Treated (95% CI)	Strength of Evidence
Withdrew because of side effects and/or lack of efficacy	**Louis, 1985[207]**	**Metoprolol**	**Clonidine**	**62**	**0.0 [12.9]**	**-8 (4 to 870)**	**-129 (1 to 257)**	**Low**
Discontinued due to side-effects	Worz, 1991[204]	Metoprolol	Bisoprolol	156	6.4 [10.3]	NS	NS	Low
Patient withdrawal due to events	Schellenberg, 2008[206]	Metoprolol	Nebivolol	30	7. [6.3]	NS	NS	Low
Drowsiness leading to withdrawal	Grotemeyer, 1990[202]	Metoprolol	Aspirin	56	7.1 [0.0]	NS	NS	Low
Gastrointestinal side-effects leading to withdrawal	**Grotemeyer, 1990[202]**	**Metoprolol**	**Aspirin**	**56**	**0.0 [17.9]**	**-6 (3 to 35)**	**-179 (28 to 329)**	**Low**
Discontinued treatment because of severe adverse reactions	**Langohr, 1985[250]**	**Clomipramine**	**Metoprolol**	**126**	**28.6 [0.0]**	**3 (3 to 6)**	**286 (173 to 399)**	**Low**

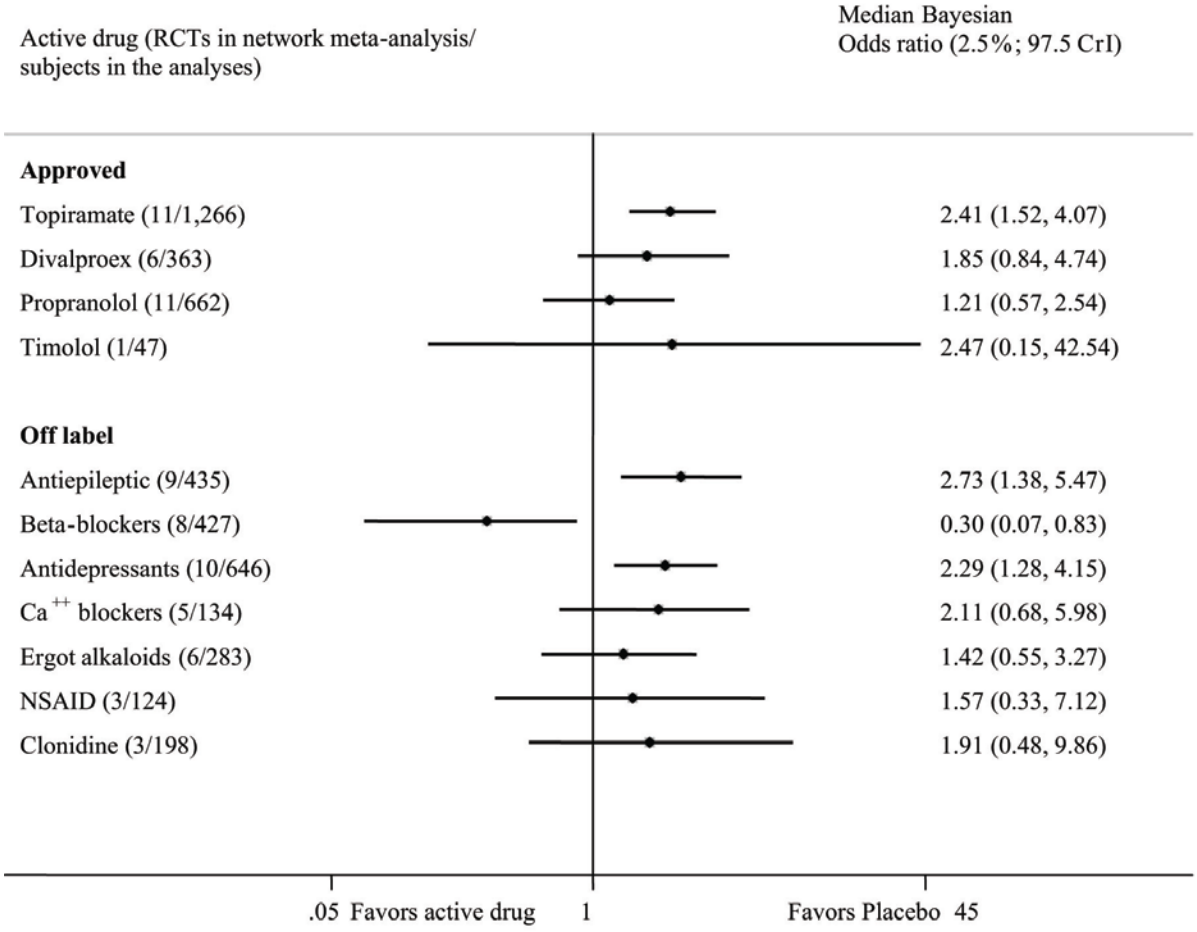
CI = confidence interval; NS = not significant
Bold = significant differences at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.
Number needed to treat and number of attributable events were calculated for statistically significant differences.

Table 31. Treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual medium risk of bias randomized controlled clinical trial[215]

Definition of the Outcome	Active Treatment	Control Treatment	Sample	Rate With Active, Percent [Control] Treatments	Number Needed To Treat (95% CI)	Attributable Events per 1,000 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]	NS	NS	Low
Withdrawn due to side effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100 mg/day	148	0.0 [5.6]	NS	NS	Low

CI = confidence interval; NS = not significant
Bold = significant differences at 95% confidence limit when 95% CI of attributable events per 1,000 treated do not include 0.
Number needed to treat and number of attributable events were calculated for statistically significant differences.

Figure 4. Bayesian network meta-analysis of treatment discontinuation due to intolerable adverse effects with drugs versus placebo (47 RCTs of 3,054 adults) in randomized controlled clinical trials that aimed episodic migraine prevention in adults



CrI = credible intervals; NSAID = nonsteroidal anti-inflammatory drugs
Note: We used heterogeneous random effects model that assumes correlation within study (rho = 0.5) and heterogeneous between studies (WinBUG codes are in the Appendix B). RCTs of angiotensin inhibiting drugs do not report intolerable adverse effects.

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

Muscle Relaxants

Onabotulinumtoxin A for Chronic Migraine

Placebo Responders

Four RCTs examined the efficacy of onabotulinumtoxin A among placebo responders versus nonresponders.[94,257-259] Onabotulinumtoxin A was better than placebo in preventing migraine attacks/month by ≥50 percent, regardless of placebo response, according to the BOTULINUM

TOXIN CDH Study Group.[94] Magnitude of the effect was slightly larger in placebo nonresponders (RR 2.2, 95% CI, 1.4 to 3.4) than in placebo responders (RR 1.6, 95% CI, 1.1 to 2.4).[94] The European BoNTA Headache Study Group demonstrated no additional benefits from increasing onabotulinumtoxin A dose, regardless of placebo response.[259] The number of migraine days did not differ by dose of onabotulinumtoxin A (75, 15, or 225U).[259]

Baseline Migraine Frequency

Onabotulinumtoxin A 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.[257] Onabotulinumtoxin A 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% CI, 0.66 to 0.92).[257]

Concurrent Prophylactic Medication Use

Onabotulinumtoxin A caused adverse effects more often than placebo (blepharoptosis, muscle weakness, and neck pain, regardless of concurrent prophylactic medication use) according to the BOTULINUM TOXIN CDH Study Group.[258]

Antiepileptics for Episodic Migraine

Topiramate

Presence of Aura

No trials directly compared drug effects in patients with and without aura. Several post hoc subgroup analysis of topiramate versus placebo trials provided conflicting evidence of the drug efficacy in respect to aura. Two publications suggested that topiramate was better than placebo in patients with aura. Post hoc subgroup analysis of one RCT found a statistically significant reduction in migraine frequency with topiramate versus placebo (-2.43 vs. -0.79 respectively, p value=0.02) only in subjects with aura.[85] Post hoc subgroup analysis of the other RCTs found that in patients with aura, topiramate was better than placebo in reducing migraine frequency, number of migraine days, severity and duration of attacks, and photophobia.[260] In contrast, however, post hoc analysis of the Prolonged Migraine Prevention found that topiramate efficacy was similar in patients with and without aura.[261]

Beta Blockers for Episodic Migraine

Propranolol

Prior Medication Use

Subgroup analysis in chronic migraine patients by prior topiramate use or overuse of the drugs for acute migraine was conducted in a single RCT.[187] This study examined adding propranolol to topiramate treatment for chronic migraine subjects for whom topiramate monotherapy had failed.[187] Propranolol with topiramate was no better than topiramate alone in reducing migraine frequency, regardless of patients' prior drug histories.[187] Quality of life score changes from baseline difference depend on prior topiramate use (Figure 5). Patients with prior stable topiramate use experienced worsening in quality of life with combined therapy versus improvement in quality of life with topiramate monotherapy. In contrast, patients without stable

prior topiramate use experienced improvement in quality of life with combined therapy versus insignificant changes with topiramate monotherapy.[187]

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.[84] Topiramate would cause a complete cessation of migraine attacks in 37 (95% CI, 8 to 67) and a reduction of monthly migraine attacks by 50 percent in 249 (95% CI, 178 to 320) per 1,000 treated women.[84] However, both men and women experienced a reduction of monthly migraine 75 to 90 percent more often with topiramate than with placebo.[84]

Gabapentin for Episodic Migraine

Presence of Aura

Gabapentin reduced the frequency and intensity of migraine attacks significantly more than placebo, regardless of aura.[262] Patients with aura experienced a slightly greater reduction in migraine frequency (mean difference -2.2, 95% CI, -2.7 to -1.7) than patients without aura (mean difference -1.6, 95% CI, -2.2 to -0.9). Patients with aura experienced a slightly greater reduction in migraine intensity (mean difference -0.83, 95%, CI, -1.12 to -0.54) than patients without aura (mean difference -0.42, 95% CI, -0.77 to -0.07).

Prior Medication Use

In a single, low-risk-of-bias RCT, gabapentin was not better than placebo in reducing acute drug use, regardless of prior use of triptans, opioids, or prescription or over-the-counter acute medications.[87]

Antidepressants for Episodic Migraine

Amitriptyline

Baseline Migraine Frequency

Amitriptyline was better than placebo in reducing monthly migraine but only in patients with baseline frequent and severe migraine (Appendix Table D164).[125] Amitriptyline was better than placebo in reducing monthly migraine only in depressed patients whose baseline migraine was frequent and severe (Appendix Table D165).[253]

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%, CI 1.45 to 3.8 for every additional day of baseline migraine) (Appendix Table D166).[228]

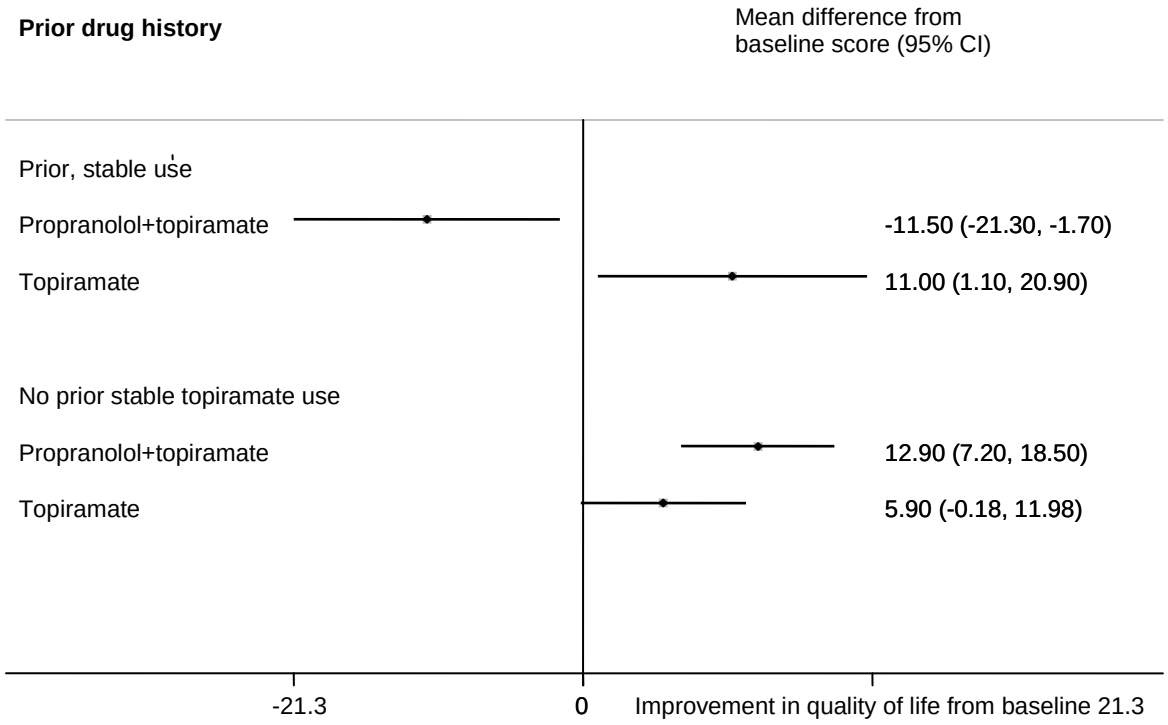
Selective Calcium Channel Blockers for Episodic Migraine

Nimodipine

Presence of Aura

A higher dose of nimodipine was not associated with increased response rates regardless of aura.[263] Nimodipine, 40 mg/day versus 20 mg/day, reduced use of drugs for acute attacks but only in patients with classic and not common migraine.[263]

Figure 5. Change from baseline in Migraine Specific Quality of Life



Migraine Specific Quality of Life = MSQL scale, an increase in MSQL indicates an improvement) with combined propranolol with topiramate or topiramate monotherapy in patients with chronic migraine for whom topiramate monotherapy failed, results from a single randomized controlled trial.[187]

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, compared with approved drugs, some off-label beta blockers and angiotensin inhibiting drugs are more effective and safer for 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 medium 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 moderate only for topiramate 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. In addition, many investigators failed to use intention-to-treat principles for all examined outcomes. Finally, many trials did not fully adhere to 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 and insufficient reporting of details.[264] 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.[2,265]

The results from eligible studies were applicable to the target population. The 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.[266] 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).[267,268] No trials examined the role of genetic polymorphism in drug metabolism and effects.[269-271] Migraine prevention trials did not address teratogenic effects, anorgasmia, impotence, and other harms of anti-epileptic drugs that can deter long-term adherence to preventive drugs. [272,273,274]

A few RCTs reported treatment effects in patient subpopulations by baseline migraine frequency of placebo response. Low-strength evidence suggested that onabotulinumtoxin A[257] and amitriptyline[228] were more effective in patients with frequent baseline migraine. Rates of migraine prevention in placebo arms ranged from 6 to 30 percent in examined RCTs. Previous research demonstrated a high placebo response in trials aimed to treat acute migraine attacks.[28,275] Our review demonstrated that a relative risk of adverse effects with onabotulinumtoxin A was lower in trials with higher placebo rates of adverse effects.[94] 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 inhibiting 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 were designed to detect significant increase in rates of bothersome adverse effects leading to treatment discontinuation when compared with placebo. In contrast, network meta-analysis demonstrated that patients stopped taking drugs more often with topiramate, off-label antiepileptics, and antidepressants than with placebo. 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.[276]

The most recent guidelines from the American Academy of Neurology and the American Headache Society recommend the four FDA-approved drugs—the antiepileptics topiramate and divalproex and the beta-blockers propranolol and timolol—for adult migraine prevention.[277] The aforementioned guidelines, which focused on published evidence, differed regarding their recommendations for off-label drugs. Further, current guidelines do not include consideration of the balance between benefits and harms of drugs as a basis for clinical decisonmaking.[278] Our review analyzed benefits and harms of drugs and provided evidence for using effective and relatively safe off-label angiotensin inhibiting drugs and other off-label beta-blockers as alternatives based on patient preferences, comorbidities, and contraindications to the medications.

We could not find published controlled observational studies about preventive drug use or about the comparative effectiveness of approved versus off-label drugs. A single retrospective administrative database study found that migraine prophylaxis medications (tricyclic antidepressants, serotonin reuptake inhibitors 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.[279] Large observational studies of health care use for migraine did not analyze comparative effectiveness of preventive drugs.[5,16]

Some evidence suggested that use of off-label drugs 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, gabapentin, and amitriptyline hydrochloride.[280] We found that off-label antiepileptics and antidepressants demonstrated worse benefits and safety profiles than beta blockers or angiotensin inhibiting drugs. Evidence of off-label drug use and associated adverse effects has been evaluated with prospective pharmacovigilance surveys in European countries.[281,282] Routine monitoring of harms with off-label drugs is needed in the United States in order to collect and analyze evidence of comparative safety 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; the cost-effectiveness of this pursuit is still being debated.[283,284] 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.

Future Research Needs

We identified gaps and biases in available evidence that can direct future research (Table 32). 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 Pharmacologic Treatments for Preventing Migraine Attacks in Adults

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

- For chronic migraine, onabotulinumtoxin A was more effective than placebo in reducing monthly chronic migraine attacks by ≥50 percent with inconsistent improvement in quality of life.
- For episodic migraine, all approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 percent (clinical response).
- Relative effect of drugs was moderate: drugs would result in clinical response in 200 to 400 patients per 1,000 treated.
- Strength of evidence was lowered due to medium risk of bias and imprecise estimates.
- Low-strength evidence from individual RCTs suggested a dose-responsive increase in migraine prevention with higher doses of onabotulinumtoxin A and topiramate (from 50-100 mg with no additional benefits with 200 mg/day).
- Among off-label drugs, pooled analyses offered low-strength evidence that the antiepileptic gabapentin, the beta-blocker metoprolol, and the calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by ≥50 percent.
- Individual RCTs offered low-strength evidence that off-label beta blockers acebutolol atenolol, and nadolol were better than placebo in reducing monthly migraine attacks by ≥50 percent. Individual RCTs demonstrated that compared with placebo, the angiotensin converting enzyme inhibitors captopril and lisinopril and the angiotensin II antagonist candesartan were better in reducing monthly migraine attacks by ≥50 percent.

Effect of Preventive Pharmacologic Treatments on Patient-Centered and Intermediate Outcomes Compared With Active Pharmacologic Treatments

- Individual RCTs provided low-strength direct evidence about the comparative effectiveness of drugs and demonstrated few significant differences.
- Indirect adjusted analysis demonstrated no differences between approved drugs and greater odds of clinical response with angiotensin II antagonist candesartan.
- Exploratory network Bayesian meta-analyses demonstrated that approved drugs were similarly better than placebo. Among off-label drug classes, angiotensin inhibiting drugs demonstrated the largest significant odds of reducing monthly migraine by ≥50 percent.

Effect of Preventive Pharmacologic Treatments on Patient-centered and Intermediate Outcomes Compared With Active Nonpharmacologic Treatments

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

Influence of Approaches to Drug Management Versus Usual Care (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 (100 percent reduction in monthly migraine attacks).
- 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 Pharmacologic Treatments for Preventing Migraine Attacks in Adults

- Among approved drugs, onabotulinumtoxin A, topiramate, and propranolol resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.
- The association was dose responsive for topiramate. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.
- Individual RCTs showed that divalproex led to treatment discontinuation, nausea, somnolence, tremor, vomiting, and asthenia.
- Among other drugs, pooled analyses demonstrated that the off-label antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo.
- Limited low-strength evidence from individual head-to-head RCTs suggested that treatment discontinuation due to adverse effects was less frequent with onabotulinumtoxin A than topiramate or amitriptyline.
- Individual unique RCTs provided low-strength direct evidence about adverse effects with specific drugs with no consistent pattern across available drug comparisons.
- Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analyses demonstrated that topiramate, off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. According to network meta-analysis, off-label angiotensin inhibiting drugs and beta blockers were the safest treatment option for adults with episodic migraine.

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

- Evidence was limited to individual RCTs that examined the drug effect modification by selected patient characteristics.
- Onabotulinumtoxin A 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 frequent and severe baseline migraine and in depressed patients with baseline severe migraine.

Table 32. Future research needs

Key Question	Findings	Types of Studies Needed To Answer Question	Future Research Recommendation
KQ 1: What are the efficacy and comparative effectiveness of pharmacologic treatments for preventing migraine attacks in adults?	• All approved drugs, some 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 59 drugs from 14 drug classes demonstrated that all approved drugs were similarly better than placebo. Among off-label drugs angiotensin inhibiting drugs, and some 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 International Headache Society 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 inhibiting drugs and beta blockers with approved antiepileptics and beta blockers. • Examine comparative effectiveness of combined treatments with approved and off-label Angiotensin inhibiting drugs vs. monotherapy. • Examine 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 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 pharmacologic and self-administrated migraine management interventions.

Table 32. Future research needs (continued)

Key Question	Findings	Types of Studies Needed To Answer Question	Future Research Recommendation
KQ 2: What are the comparative harms from pharmacologic treatments for preventing migraine attacks in adults?	• Among approved drugs, onabotulinumtoxin A, topiramate, and propranolol resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. • The association was dose responsive for topiramate. Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss. • Individual RCTs showed that divalproex led to treatment discontinuation due to adverse effects that included nausea, somnolence, tremor, vomiting, and asthenia. • Among other drugs, pooled analyses demonstrated that off-label antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo.	• Randomized clinical trials. • Creating 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 and safe angiotensin inhibiting 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.

Table 32. Future research needs (continued)

Key Question	Findings	Types of Studies Needed To Answer Question	Future Research Recommendation
KQ 2: What are the comparative harms from pharmacologic treatments for preventing migraine attacks in adults? (continued)	• Limited low-strength evidence from individual head-to-head RCTs suggested that treatment discontinuation due to adverse effects was less frequent with onabotulinumtoxin A than topiramate or amitriptyline. • Individual unique RCTs provided low-strength direct evidence about adverse effects with specific drugs, with no consistent pattern across available drug comparisons. • Indirect adjusted analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analyses demonstrated that topiramate, off-label antiepileptics, and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo. According to network meta-analysis, off-label angiotensin inhibiting drugs and beta-blockers were the safest treatment option for adults with episodic migraine		

Table 32. Future research needs (continued)

Key Question	Findings	Types of Studies Needed To Answer Question	Future Research Recommendation
KQ 3: Which patient characteristics predict the effectiveness and safety of pharmacologic 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 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.

RCT = randomized controlled trial

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Appendix A. Literature Search

January, 2011
PubMed

#	Strings	N
8	Search "Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh] Limits: Humans, Meta-Analysis, English	97
7	Search "Migraine Disorders"[Mesh] AND "Migraine Disorders"[Mesh] Limits: Humans, Randomized Controlled Trial, English	907

#	Strings	N
71	Search migraine NOT acute Limits: Humans, Randomized Controlled Trial, English	655
70	Search migraine Limits: Humans, Randomized Controlled Trial, English	1040
66	Search melatonin AND migraine	55
67	Search melatonin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	7
64	Search "Brain-Derived Neurotrophic Factor"[Mesh] AND migraine	6
63	Search "Brain-Derived Neurotrophic Factor"[Mesh] AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	1
62	Search "Brain-Derived Neurotrophic Factor"[Mesh] Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	94
58	Search Risperidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
57	Search Paliperidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
56	Search Methiothepin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
55	Search Metergoline AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
53	Search Lisuride AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	5
51	Search Bromocriptine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	4
50	Search Zotepine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
49	Search Ziprasidone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
48	Search Trifluoperazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
47	Search Tenilapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
46	Search Sulpiride AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	1
45	Search Spiperone AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
44	Search Sertindole AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
43	Search Olanzapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
42	Search Loxapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
41	Search Ketanserin AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
40	Search Imipramine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
39	Search Fluperlapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
38	Search Fluphenazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
36	Search Cyproheptadine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	9
35	Search Clozapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
33	Search Clomipramine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	2
32	Search Aripiprazole AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
31	Search Amoxapine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	0
29	Search Amitriptyline AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	34
28	Search Amitriptyline AND migraine Limits: Humans, English	150
27	Search 5-HT7 AND migraine Limits: Humans, English	12
24	Search 5-HT7 Limits: Humans, English	150
13	Search Quetiapine AND migraine Limits: Humans, English	5
21	Search "Antipsychotic Agents "[Pharmacological Action] AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English	41

20	Search "Antipsychotic Agents "[Pharmacological Action] AND migraine Limits: Humans, English	206
19	Search "Antipsychotic Agents "[Pharmacological Action] Limits: Humans, English	51308
11	Search 5-HT2A AND migraine Limits: Humans, English	14
10	Search 5-HT2A antagonists AND migraine Limits: Humans, English	3
7	Search 5-HT2A antagonists Limits: Humans, English	394
5	Search Alpha-2 agonists AND migraine Limits: Humans, English	6
4	Search Alpha-2 agonists AND migraine	17

84	**Search telcagepant AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**4**
83	**Search olcegepant AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
82	**Search Arachidonic cascade modulators Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
80	**Search tonabersat) AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**6**
79	**Search dextromethorphan AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
78	**Search dextromethorphan AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
77	**Search loxapine AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**0**
76	**Search prochlorperazine AND migraine NOT acute Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**8**
75	**Search prochlorperazine AND migraine Limits: Humans, Clinical Trial, Randomized Controlled Trial, English**	**20**

August, 2011

#	Strings	N
15	Search Phenelzine AND migraine Limits: Humans, Journal Article, English	11
14	Search Bupropion AND migraine Limits: Humans, Journal Article, English	1
13	Search Imipramine AND migraine Limits: Humans, Journal Article, English	15
12	Search Imipramine AND headache Limits: Humans, Journal Article, English	60
11	Search Doxepin AND headache Limits: Humans, Journal Article, English	15
9	Search Desipramine AND headache Limits: Humans, Journal Article, English	13
10	Search Desipramine AND migraine Limits: Humans, Journal Article, English	1
7	Search Protriptyline AND headache Limits: Humans, Journal Article, English	4
6	Search Protriptyline AND migraine Limits: Humans, Journal Article, English	0

Updated search in Ovid; 1948 to November Week 3 2011

#	Searches	Results
1	exp migraine disorders/dt	5944
2	exp migraine disorders/pc	1669
3	ad.fs.	998247
4	2 and 3	286
5	1 or 4	6112
6	1 or 2	7065
7	exp "off-label use"/	519
8	off label.mp.	2412
9	7 or 8	2412
10	6 and 9	14
11	exp calcium channel blockers/	68976
12	exp antihypertensive agents/	216956
13	exp antidepressive agents/	113058
14	exp anticonvulsants/	111349
15	exp botulinum toxin type a/	4832
16	exp alzheimer disease/dt	8107

17	11 or 12 or 13 or 14 or 15 or 16	476372
18	6 and 17	1675
19	5 or 10 or 18	6489
20	limit 19 to (humans and yr="2000 -Current")	3195
21	limit 20 to updaterange="mesz(20111121020154-20111121091315]"	0

Ovid MEDLINE(R) 1946 to December Week 4 2011

#	Searches	Results
1	exp migraine disorders/dt	5882
2	exp migraine disorders/pc	1659
3	ad.fs.	975844
4	2 and 3	284
5	1 or 4	6048
6	1 or 2	6996
7	exp "off-label use"/	510
8	off label.mp.	2358
9	7 or 8	2358
10	6 and 9	13
11	exp calcium channel blockers/	67571
12	exp antihypertensive agents/	1420023
13	exp antidepressive agents/	110836
14	exp anticonvulsants/	1012405
15	exp botulinum toxin type a/	4648
16	exp alzheimer disease/dt	7829
17	11 or 12 or 13 or 14 or 15 or 16	2510533
18	6 and 17	1831
19	5 or 10 or 18	6431

Database(s): **Ovid MEDLINE(R)** 1946 to May Week 2 2012
Search Strategy:

#	Searches	Results
1	drug management.mp.	467
2	exp patient care team/	49789
3	exp delivery of health care, integrated/	7185
4	integrated care.mp.	1087
5	exp managed care programs/	38113
6	(managed care or coordinated care).mp.	28360
7	exp Patient Education as Topic/	64554
8	exp Health Education/	125606
9	drug surveillance.mp.	432
10	exp drug monitoring/	12104
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	231287
12	exp patient compliance/	46268
13	exp patient satisfaction/	52327
14	exp patient care management/	475066
15	12 or 13 or 14	555310
16	exp migraine disorders/dt	5965
17	11 and 16	111
18	15 and 16	360

Ovid Technologies, Inc.

Search for: limit 19 to (humans and yr="2000 -Current")
Results: 100

Database: Ovid MEDLINE(R) <1946 to May Week 2 2012> Search Strategy:
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1 exp migraine disorders/dt (5965)
2 exp migraine disorders/pc (1692)
3 ad.fs. (1002489)
4 2 and 3 (291)
5 1 or 4 (6136)
6 1 or 2 (7101)
7 exp "off-label use"/ (628)
8 off label.mp. (2572)
9 7 or 8 (2572)
10 6 and 9 (14)
11 exp calcium channel blockers/ (68722)
12 exp antihypertensive agents/ (217035)
13 exp antidepressive agents/ (113333)
14 exp anticonvulsants/ (112028)
15 exp botulinum toxin type a/ (4853)
16 exp alzheimer disease/dt (8211)
17 11 or 12 or 13 or 14 or 15 or 16 (477138)
18 6 and 17 (1689)
19 5 or 10 or 18 (6514)
20 limit 19 to (humans and yr="2000 -Current") (3226)

Scientific Information Package requests and responses

Company Name	Date Responded
Abbott Laboratories	No response
Alexza Pharmaceuticals, Inc.	No response
Allergan, Inc.	No response
Almirall, S.A.	No response
AstraZeneca Pharmaceuticals, LP	No response
Beth Israel Deaconess Medical Center	No response
Boston Scientific	No response
BTG International, Ltd.	No response
Capnia, Inc.	No response
Centre Hospitalier Universitaire de Saint Etienne	No response
Cephalon, Inc	No response
Chengdu University of Traditional Chinese Medicine	No response
Clinvest	No response
CoLucid Pharmaceuticals, Inc.	No response
D-Pharm Ltd.	No response
Eisai Inc.	No response
Eli Lilly & Co	No response
Endo Pharmaceuticals	No response
eNeura	No response
Eurohead	No response
GlaxoSmithKline	Submitted
HaEmek Medical Center	No response
Ipsen Biopharm, Ltd	No response
Janssen Cilag Pharmaceutica S.A.C.I.	No response
Janssen EMEA	No response
Janssen Pharmaceutica NV	Submitted
Janssen-Ortho, Inc.	No response
Johnson & Johnson Pharmaceutical Research & Development, L.L.C.	No response
Kowa Pharmaceuticals America	No response
Lotus Pharmaceuticals, Inc.	No response
Luitpold Pharmaceuticals, Inc.	No response
Manhattan Pharmaceuticals, Inc.	No response
MAP Pharmaceuticals, Inc.	No response
Medtronic, Inc.	No response
Merck & Co., Inc.	Submitted
Nektar	Nothing to submit 11/16/2011
NeurAxon	No response
Nordlandssykehuset HF	No response
Novartis Pharmaceuticals Corporation	No response
NPS Pharmaceuticals	No response
Ortho-McNeil Janssen Scientific Affairs, LLC	No response
Ortho-McNeil Neurologics	No response
Ortho-McNeil-Janssen Pharmaceuticals, Inc	No response
Pfizer Inc	No response
Pozen	No response
PriCara® (Division of Ortho-McNeil-Janssen Pharmaceuticals, Inc.)	No response
Raptor Pharmaceutical Corp.	No response
Roxane Laboratories	No response
SK Chemicals	No response
Sorlandet Hospital HF	No response
Takeda Global Research & Development Center, Inc.	No response
Takeda Pharmaceuticals North America, Inc.	No response
The EMMES Corporation	No response
UCB, Inc.	No response
Valeant Pharmaceuticals International	No response
Zogenix	No response

Appendix B. Analytical Framework

PICOTS Framework

Population(s)

Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society[1] (see below for definitions).

Patient characteristics that can modify the effects of pharmacological treatments for preventing migraine attacks in children and adults:

- Age
- Sex
- Pregnancy
- Hormone-based birth control and hormone replacement
- The onset of menarche and menopause
- Race and ethnicity
- Socioeconomic status
- Education
- Family history
- Access to care, type of care, and residence in rural or urban areas
- Definition of migraine
- Presence of aura
- Headache frequency
- Prior treatments; overuse of drugs for acute migraine
- Obesity
- Nutritional and dietary factors, specifically caffeine
- Aerobic fitness
- Previous head injury
- Psychological factors and social/family support system
- Comorbidities (depression, bipolar disorder, anxiety, diabetes, hypertension, cardiovascular diseases, others)
- Concomitant medications for comorbid conditions

Interventions

Drugs approved by the FDA (such as propranolol, timolol, topiramate, and divalproex sodium) to prevent episodic migraine and to treat chronic migraine (such as Botox).

Off-label medications available in the United States and previously examined in clinical trials for preventing migraine.

Monotherapy.

Multidrug interventions.

Combined pharmacological with nonpharmacological modalities: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Comparators

Placebo.
Drug treatments (comparative effectiveness).
Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements.

Outcomes

Patient-centered outcomes:
- Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review.
- Quality of life.
- Patient satisfaction.
- Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes.
- Emergency visits, loss of work days; treatment failure.

Intermediate outcomes:
- Number of headache days.
- Number of moderate to severe headache days.
- Improvement in associated symptoms.
- Use of drugs for acute migraine (prescribed or over-counter).
- Physician/healthcare professional (HCP) visits.

Harms:
- All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness).
- Treatment discontinuation due to adverse effects.
- Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).

Timing

6 months or more; optimally 12 months.
Any time of occurrence for the harms.

Setting

Outpatient settings

Definition of Terms

Migraine (as defined by the Headache Classification Subcommittee of the International Headache Society):[1]

Repeated attacks of headache lasting 4 to 72 hours in patients with a normal physical examination, no other reasonable cause for the headache, and:

At least two of the following features:
- Unilateral pain
- Throbbing pain

- Aggravation by movement
- Moderate or severe intensity

Plus at least one of the following features:

- Nausea/vomiting
- Photophobia and phonophobia

Episodic migraine as an indication for preventive treatment:

Five or more attacks a month[2]

Three or more attacks a month[2]

Definitions of chronic migraine (can be chronic from onset or transformed from episodic migraine):

FDA:

- Chronic migraine is defined as having a history of migraine and experiencing a headache on most days of the month.[3]

Revised International Headache Society criteria for chronic migraine:[1]

1.5.1. Chronic migraine

A. Headache (tension-type and/or migraine) on ≥15 days per month for at least 3 months
   * Characterization of a frequently recurring headache generally requires a headache diary to record information on pain and associated symptoms day by day for at least 1 month.
B. Occurring in a patient who has had at least five attacks.
C. On ≥8 days per month for at least 3 months headache has fulfilled C.1 and/or C.2 below, that is, has fulfilled criteria for pain and associated symptoms of migraine without aura.
   1. Has at least two of a–d
      a. Unilateral location
      b. Pulsating quality
      c. Moderate or severe pain intensity
      d. Aggravation by or causing avoidance of routine physical activity (e.g., walking or climbing stairs) and at least one of (1) or (2):
         (1). Nausea and/or vomiting
         (2). Photophobia and phonophobia
   2. Treated and relieved by triptan(s) or ergot before the expected development of C.1 above
D. No medication overuse† and not attributed to another causative disorder
   †Headache Classification Committee criteria for a medication overuse headache (A8.2)[1]

References

1. 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.
2. 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.
3. Administration USFaD. FDA News Release: FDA approves Botox to treat chronic migraine. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm229782.htm. Accessed on February 1 2011.

Table 1. Pharmacological classes for migraine prevention

Drug, ATC Code*	Class of Drug
ANTIEPILEPTICS	
Topiramate, N03AX11	N03 ANTIEPILEPTICS N03AX Other antiepileptics
Lamotrigine, N03AX09	N03A ANTIEPILEPTICS
Levetiracetam, N03AX14	N03A ANTIEPILEPTICS
Pregabalin, N03AX16	N03A ANTIEPILEPTICS alpha2-delta agonist
Carbamazepine , N03AF01	N03A ANTIEPILEPTICS N03AF Carboxamide derivatives
Valproic acid, N03AG01	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, Gamma-aminobutyric acid (GABA) enhancer and analog
Vigabatrin, N03AG04	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, GABA transaminase inhibitor
Tiagabine, N03AG06	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives, gamma aminobutyric acid (GABA) enhancer
Zonisamide, N03AX15	N03A ANTIEPILEPTICS N03AX Other antiepileptics
Valproate	N03A ANTIEPILEPTICS N03AG Fatty acid derivatives
Divalproex	Gamma-aminobutyric acid (GABA) enhancer and analog
Gabapentin, N03AX12	N03A ANTIEPILEPTICS
Acetazolamide, S01EC01	S01EC, carbonic anhydrase inhibitor
ANTIDEPRESSANTS	
Nortriptyline , N06AA10	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Clomipramine, N06AA04	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Citalopram, N06AB04	N06A ANTIDEPRESSANTS N06AB selective serotonin reuptake inhibitors
Venlafaxine, N06AX16	N06A ANTIDEPRESSANTS N06AX Other antidepressants
Amitriptyline	N06A ANTIDEPRESSANTS N06AA nonselective monoamine reuptake inhibitors
Mirtazapine, N06AX11	N06A ANTIDEPRESSANTS tricyclic antidepressants
BETA BLOCKERS	
Timolol, C07AA06	C07AA , Beta blocking agents, nonselective
Nadolol , C07AA12	C07AA Beta blocking agents, nonselective
Propranolol,C07AA05	C07AA Beta blocking agents, nonselective
Metoprolol,C07AB02	C07AB Beta blocking agents, selective
Atenolol, C07AB03	C07AB Beta blocking agents, selective
Bisoprolol,C07AB07	C07AB Beta blocking agents, selective
Acebutolol,C07AB04	C07AB Beta blocking agents, selective
Alprenolol, C07AA01	C07A BETA BLOCKING AGENTS
Oxprenolol, C07AA02 (discontinued in the FDA)	C07AA Beta blocking agents, nonselective
Pindolol, C07AA03	C07AA Beta blocking agents, nonselective
ACE INHIBITORS	
Trandolapril, C09AA10	C09AA ACE inhibitors
Enalapril,C09AA02	C09AA ACE inhibitors
Captopril,C09AA01	C09AA ACE inhibitors
Lisinopril, C09AA03	C09AA ACE inhibitors
ANGIOTENSIN II ANTAGONISTS	
Telmisartan,C09CA07	C09CA Angiotensin II antagonists
Candesartan, C09CA06	C09CA Angiotensin II antagonists
CALCIUM CHANNEL ANTAGONIST	
Dotarizine	SELECTIVE CALCIUM CHANNEL ANTAGONIST; 5-HT receptors ANTAGONIST
Flunarizine, N07CA03; Sibelium	SELECTIVE CALCIUM CHANNEL ANTAGONISTN07C ANTIVERTIGO PREPARATIONS

Drug, ATC Code*	Class of Drug
SELECTIVE CALCIUM CHANNEL BLOCKERS	
Nimodipine,C08CA06	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Verapamil,C08DA01	C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS C08DA Phenylalkylamine derivatives
Nicardipine,C08CA04	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
Nifedipine,C08CA05	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08CA Dihydropyridine derivatives
ANTIADRENERGICS	
Clonidine,C02AC01	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
Labetalol, C07AG01	C07AG , Alpha and beta blocking agents
Dixarit (clonidine, C02AC01) Guanfacine, C02AC02	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02AC Imidazoline receptor agonists
ANTI-DEMENTIA	
Donepezil, N06DA02	N06 PSYCHOANALEPTICS
Memantine, N06DX01	N06D ANTI-DEMENTIA DRUGS N-methyl-D-aspartate (NMDA) receptor inhibitor
ANTIPSYCHOTICS	
Aripiprazole,N05AX12	N05A ANTIPSYCHOTICS
Olanzapine,N05AH03	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Quetiapine,N05AH04	N05A ANTIPSYCHOTICS N05AH Diazepines, oxazepines, thiazepines and oxepines
Deanxit (Flupentixol, N05AF01)	N05A ANTIPSYCHOTICS N05AF Thioxanthene derivatives
Sulpiride, N05AL01 (antipsychotic)	N05A ANTIPSYCHOTICS N05AL Benzamides
Prochlorperazine, N05AB04	N05A ANTIPSYCHOTICS
DOPAMINERGIC AGENTS	
Amantadine, N04BB01	N04B DOPAMINERGIC AGENTS N04BB Adamantane derivatives N-methyl-D-aspartate (NMDA) receptor inhibitor
Dihydroergocryptine, N04BC03	N04B DOPAMINERGIC AGENTS N04BC Dopamine agonists
ERGOT ALKALOIDS	
Dihydroergotamine, N02CA01	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Lisuride, N02CA07 Ergotamine, N02CA02	N02C ANTIMIGRAINE PREPARATIONS N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
Methysergide, N02CA04	N02C ANTIMIGRAINE PREPARATIONS N02CA Ergot alkaloids
MUSCLE RELAXANTS	
Botulinum Toxin Type A, M03AX01	M03A MUSCLE RELAXANTS, PERIPHERALLY ACTING AGENTS M03AX Other muscle relaxants, peripherally acting agents
Tizanidine, M03BX02	M03B MUSCLE RELAXANTS, CENTRALLY ACTING AGENTS
SYSTEMIC DRUGS	
Montelukast, R03DC03	R03D OTHER SYSTEMIC DRUGS FOR OBSTRUCTIVE AIRWAY DISEASES R03DC Leukotriene receptor antagonists

ATC code - The Anatomical Therapeutic Chemical classification

Table 2 Bayesian models summary under the noninformative prior

Fixed effect model	Random effect model (homogeneous)	Random effect model (heterogeneous)	Random effect model (inconsistency)
Data $r_{ik} \sim Bin(n_{ik}, p_{ik})$ i = 1, …, NS; k = 1, …, NT (NS = number of study; NT = number of trt) **Model** $logit(p_{ik}) = \mu_{iB} + \Delta_{Bk}$ where B is for the baseline treatment, μ_{iB} is the log odds of the baseline treatment and Δ_{Bk} is the fixed effect of the k^{th} drug versus the baseline treatment defined by $d_k - d_B$ with the fixed effect of the k^{th} drug versus placebo, d_k ($d_B = 0$) **Prior** $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{iBk} is the random effect of the k^{th} drug versus the baseline treatment in the i^{th} study **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $\sigma \sim Unif(0.01,2)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{iBk} is the random effect of the k^{th} drug versus the baseline treatment in the i^{th} study **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma_{Bk}^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $log\sigma_{xy} = log\sigma_0 + v_{xy}$ $\sigma_0 \sim Unif(0.01,2)$ $v_{xy} \sim N(0, \psi^2)$	**Data** $r_{ik} \sim Bin(n_{ik}, p_{ik})$ **Model** $logit(p_{ik}) = \mu_{iB} + \delta_{iBk}$ where δ_{ik} is the random effect of the k^{th} drug versus the placebo in the i^{th} study 1. $d_{BC} = d_{AC} - d_{AB} + w_{ABC}$ w_{ABC} is the amount of inconsistency between direct and indirect comparisons **Prior** $\delta_{iBk} \sim N(d_k - d_B, \sigma^2)$ $d_k \sim N(0, 10000)$ $\mu_{iB} \sim N(0, 10000)$ $w_{ABC} \sim N(0, \sigma_w^2)$ $\sigma, \sigma_w \sim Unif(0.01,2)$
[Example] Study 1: Drugs 1 vs. 2 vs. 3 trial (drug 1 is the baseline treatment)			
Fixed effect model	**Random effect model (homogeneous)**	**Random effect model (heterogeneous)**	**Random effect model (inconsistency)**
Data $r_{11} \sim Bin(n_{11}, p_{11})$ $r_{12} \sim Bin(n_{12}, p_{12})$ $r_{13} \sim Bin(n_{13}, p_{13})$ **Model** 2. $logit(p_{11}) = \mu_{11}$ 3. $logit(p_{12}) = \mu_{11} + d_2$ 4. $logit(p_{13}) = \mu_{11} + d_3$ **Prior** $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$	**Model** 5. $logit(p_{11}) = \mu_{11}$ 6. $logit(p_{12}) = \mu_{11} + \delta_{12}$ 7. $logit(p_{13}) = \mu_{11} + \delta_{13}$ **Prior (assume ρ=0.5)** $\begin{pmatrix}\delta_{12}\\ \delta_{13}\end{pmatrix} \sim MVN(\begin{pmatrix}d_2\\ d_3\end{pmatrix}, \sigma^2 \begin{pmatrix}1 & 0.5\\ 0.5 & 1\end{pmatrix})$ ➔ $\delta_{12} \sim N(d_2, \sigma^2)$ ➔ $\delta_{13} \mid \delta_{12} \sim N(d_3 + \frac{1}{2}(\delta_{12} - d_2), \frac{3}{4}\sigma^2)$ $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$ $\sigma \sim Unif(0.01,2)$	**Model** 8. $logit(p_{11}) = \mu_{11}$ 9. $logit(p_{12}) = \mu_{11} + \delta_{12}$ 10. $logit(p_{13}) = \mu_{11} + \delta_{13}$ **Prior (assume ρ=0.5)** $\begin{pmatrix}\delta_{12}\\ \delta_{13}\end{pmatrix} \sim MVN(\begin{pmatrix}d_2\\ d_3\end{pmatrix}, \begin{pmatrix}\sigma_{11}^2 & 0.5\sigma_{12}\\ 0.5\sigma_{12} & \sigma_{22}^2\end{pmatrix})$ ➔ $\delta_{12} \sim N(d_2, \sigma_1^2)$ ➔ $\delta_{13} \mid \delta_{12} \sim N(d_3 + \frac{1}{2}(\delta_{12} - d_2), \frac{3}{4}\sigma_2^2)$ $d_2, d_3 \sim N(0, 10000)$ $\mu_{11} \sim N(0, 10000)$ $log\sigma_{11} = log\sigma_0 + v_{11}$ $log\sigma_{12} = log\sigma_0 + v_{12}$ $log\sigma_{22} = log\sigma_0 + v_{22}$ $\sigma_0 \sim Unif(0.01,2)$ $v_{11}, v_{12}, v_{22} \sim Unif(0.01, \psi^2)$	Study 1: 1 vs. 2 vs. 3 trial 11. Study 2: 1 vs. 2 12. Study 3: 1 vs. 3 ➔ We can estimate w_{123} because the data permit estimation via the equation $d_{23} = d_{13} - d_{13} + w_{123}$ Model and priors are similarly defined as in Model2. Additional prior is $w_{123} \sim N(0, \sigma_w^2)$ $\sigma_w \sim Unif(0.01,2)$

Table 3. Winbug Code for Bayesian network meta analysis

```
Outcome – reduction in monthly migraine by ≥50% or perceived clinically important treatment success
# Model - heterogeneous random effects model
# Assume correlation within study (rho = 0.5)
# Assume heterogeneous between studies

model {
  for (i in 1:NS) {
    s[i,1] <- 0
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(mmu[t[i,1]], taumu)  # handle different baseline treatments

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau[t[i,1],t[i,k]]*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  mmu[5] <- 0    #Treatments 1,2,3,4,6,7 are one of baseline treatments.
  mmu[8] <- 0    # other treatments should be assigned to 0.
  mmu[9] <- 0
  mmu[10] <- 0
  mmu[11] <- 0
mmu[12] <- 0
mmu[13] <- 0
mmu[14] <- 0
  mmu[1] ~ dnorm(0, 0.0001)
  mmu[2] ~ dnorm(0, 0.0001)
  mmu[3] ~ dnorm(0, 0.0001)
  mmu[4] ~ dnorm(0, 0.0001)
  mmu[6] ~ dnorm(0, 0.0001)
  mmu[7] ~ dnorm(0, 0.0001)
  sdmu ~ dunif(0.01, 2)
  taumu <- 1/pow(sdmu,2)

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0,0.0001)
    ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

  for(i in 1:(NT-1)) {
    for(j in (i+1):NT) {
      v[i,j] ~ dnorm(0, 8.32)
      log(sd[i,j]) <- log(sd0) + v[i,j]
      tau[i,j] <- 1/pow(sd[i,j],2)
      var[i,j] <- pow(sd[i,j],2)
    }
  }
  sd0 ~ dunif(0.01, 2)
  var0 <- pow(sd0,2)
```

```
  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mmu[1]  # "mP" means the odds of placebo.

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0,    0,0,0,0),
sd0=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,    0,0,0,0,0,  0,0),
mmu=c(0,0,0,0,NA, 0,0,NA,NA,NA, NA,NA,NA,NA), sdmu=1
)


#Data


#Data
list(NT=14, NS=97)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
17	83	34	83	NA	1	1	4	NA	2
18	61	26	55	NA	1	1	8	NA	2
0	14	2	14	NA	1	1	7	NA	2
15	22	14	22	NA	1	3	14	NA	2
24	48	31	46	NA	1	4	14	NA	2
1	16	6	16	NA	1	1	8	NA	2
45	75	44	74	NA	1	7	14	NA	2
818	11034	661	11037	NA	1	1	6	NA	2
3	28	14	28	NA	1	6	7	NA	2
12	20	6	20	NA	1	4	12	NA	2
5	44	18	47	NA	1	4	7	NA	2
16	77	29	77	NA	1	1	7	NA	2
9	15	5	13	NA	1	4	7	NA	2
12	54	10	54	NA	1	4	8	NA	2
10	31	8	31	NA	1	7	11	NA	2
5	19	6	19	NA	1	1	6	NA	2

5	48	26	48	NA	1	1	9	NA	2
4	18	10	17	NA	1	1	14	NA	2
12	48	48	96	NA	1	1	4	NA	2
10	47	25	47	NA	1	1	4	NA	2
15	36	17	36	NA	1	4	7	NA	2
3	15	1	14	NA	1	4	8	NA	2
4	37	10	34	NA	1	1	7	NA	2
3	13	13	25	NA	1	1	4	NA	2
13	23	8	23	NA	1	4	11	NA	2
5	37	33	70	NA	1	1	3	NA	2
6	43	17	43	NA	1	1	3	NA	2
7	23	16	23	NA	1	1	6	NA	2
7	32	14	36	NA	1	1	13	NA	2
10	34	10	35	NA	1	1	13	NA	2
2	15	19	44	NA	1	1	3	NA	2
24	37	25	37	NA	1	3	4	NA	2
0	60	14	60	NA	1	1	5	NA	2
5	45	26	98	NA	1	1	9	NA	2
34	69	32	66	NA	1	11	14	NA	2
61	135	40	135	NA	1	6	7	NA	2
2	21	5	19	NA	1	1	2	NA	2
9	27	8	26	NA	1	1	9	NA	2
125	270	141	275	NA	1	4	14	NA	2
32	116	50	123	NA	1	1	3	NA	2
2	60	23	60	NA	1	1	5	NA	2
1	14	10	14	NA	1	1	2	NA	2
18	84	23	93	NA	1	1	13	NA	2
112	200	112	184	NA	1	1	10	NA	2
12	57	37	58	NA	1	1	2	NA	2
0	19	9	21	NA	1	1	8	NA	2
93	372	188	386	NA	1	1	2	NA	2
20	22	21	22	NA	1	2	3	NA	2
25	73	55	140	NA	1	1	2	NA	2
16	372	8	384	NA	1	1	2	NA	2
0	27	7	32	NA	1	1	2	NA	2
8	13	8	15	NA	1	2	9	NA	2
27	45	30	45	NA	1	2	13	NA	2
31	85	28	85	NA	1	1	9	NA	2
37	58	41	67	NA	1	3	13	NA	2
24	65	24	59	NA	1	1	13	NA	2
99	178	78	169	NA	1	2	8	NA	2

50	163	64	165	NA	1	1	2	NA	2
11	25	7	24	NA	1	4	8	NA	2
6	16	18	53	NA	1	1	4	NA	2
48	197	47	194	NA	1	1	8	NA	2
16	40	15	40	NA	1	2	9	NA	2
8	84	20	91	NA	1	1	6	NA	2
0	11	5	8	NA	1	1	4	NA	2
0	28	3	28	NA	1	1	7	NA	2
2	43	13	43	NA	1	1	7	NA	2
2	31	14	31	NA	1	1	6	NA	2
0	8	6	24	NA	1	1	7	NA	2
0	33	10	33	NA	1	1	12	NA	2
8	34	12	35	NA	1	4	14	NA	2
2	29	8	29	NA	1	1	14	NA	2
17	71	20	72	NA	1	1	14	NA	2
4	36	20	36	NA	1	1	12	NA	2
0	17	5	17	NA	1	4	14	NA	2
4	30	8	30	NA	1	1	12	NA	2
19	75	28	75	NA	1	1	10	NA	2
24	54	14	48	NA	1	11	14	NA	2
7	36	16	37	NA	1	1	8	NA	2
12	33	11	33	NA	1	1	7	NA	2
1	13	3	11	NA	1	4	8	NA	2
0	29	5	29	NA	1	1	14	NA	2
1	40	17	40	NA	1	1	6	NA	2
0	12	8	12	NA	1	1	5	NA	2
1	14	2	14	NA	1	4	13	NA	2
0	30	10	30	NA	1	1	11	NA	2
11	35	10	38	NA	1	1	6	NA	2
6	14	6	18	NA	1	11	14	NA	2
12	22	18	23	NA	1	1	9	NA	2
16	32	13	27	NA	1	4	14	NA	2
11	47	16	48	NA	1	1	5	NA	2
0	24	8	24	NA	1	1	7	NA	2
10	20	40	62	NA	1	1	9	NA	2
8	36	58	112	NA	1	1	2	NA	2
0	19	6	22	0	17	4	7	12	3
11	49	50	144	62	144	1	2	4	3
18	60	38	60	28	60	1	2	9	3
13	50	21	50	22	50	1	7	11	3

END

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
best1[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[2]	0.0018	0.04239	7.992E-4	0.0	0.0	0.0	50001	5000
best1[3]	0.053	0.224	0.004245	0.0	0.0	1.0	50001	5000
best1[4]	0.0014	0.03739	5.815E-4	0.0	0.0	0.0	50001	5000
best1[5]	0.7118	0.4529	0.01115	0.0	1.0	1.0	50001	5000
best1[6]	0.01	0.0995	0.001563	0.0	0.0	0.0	50001	5000
best1[7]	0.027	0.1621	0.002892	0.0	0.0	1.0	50001	5000
best1[8]	0.0018	0.04239	5.62E-4	0.0	0.0	0.0	50001	5000
best1[9]	0.0016	0.03997	6.033E-4	0.0	0.0	0.0	50001	5000
best1[10]	0.0048	0.06912	0.001058	0.0	0.0	0.0	50001	5000
best1[11]	0.1004	0.3005	0.006587	0.0	0.0	1.0	50001	5000
best1[12]	0.0584	0.2345	0.007058	0.0	0.0	1.0	50001	5000
best1[13]	4.0E-4	0.02	2.817E-4	0.0	0.0	0.0	50001	5000
best1[14]	0.0276	0.1638	0.003541	0.0	0.0	1.0	50001	5000
best2[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[2]	0.0096	0.09751	0.001736	0.0	0.0	0.0	50001	5000
best2[3]	0.1468	0.3539	0.007527	0.0	0.0	1.0	50001	5000
best2[4]	0.0162	0.1262	0.002781	0.0	0.0	0.0	50001	5000
best2[5]	0.117	0.3214	0.005758	0.0	0.0	1.0	50001	5000
best2[6]	0.0454	0.2082	0.003424	0.0	0.0	1.0	50001	5000
best2[7]	0.149	0.3561	0.009166	0.0	0.0	1.0	50001	5000
best2[8]	0.0074	0.0857	0.001582	0.0	0.0	0.0	50001	5000
best2[9]	0.008	0.08908	0.001439	0.0	0.0	0.0	50001	5000
best2[10]	0.011	0.1043	0.001426	0.0	0.0	0.0	50001	5000
best2[11]	0.2504	0.4332	0.009641	0.0	0.0	1.0	50001	5000
best2[12]	0.12	0.325	0.008177	0.0	0.0	1.0	50001	5000
best2[13]	0.0028	0.05284	0.001012	0.0	0.0	0.0	50001	5000
best2[14]	0.1164	0.3207	0.006902	0.0	0.0	1.0	50001	5000
d[2]	0.9084	0.1925	0.004303	0.5261	0.9094	1.281	50001	5000
d[3]	1.185	0.2705	0.009589	0.6785	1.175	1.726	50001	5000
d[4]	1.055	0.1783	0.006629	0.712	1.054	1.422	50001	5000
d[5]	1.776	0.4397	0.01533	0.9306	1.767	2.685	50001	5000
d[6]	0.9348	0.2981	0.007378	0.3516	0.9321	1.54	50001	5000
d[7]	1.226	0.2077	0.007711	0.8384	1.216	1.668	50001	5000
d[8]	0.7579	0.2531	0.007698	0.2864	0.7527	1.279	50001	5000
d[9]	0.7709	0.2503	0.007164	0.2765	0.7705	1.26	50001	5000
d[10]	0.4083	0.4418	0.008455	-0.4678	0.4051	1.321	50001	5000
d[11]	1.297	0.2976	0.009451	0.7107	1.297	1.87	50001	5000
d[12]	0.9983	0.4622	0.01963	-0.003467	1.02	1.843	50001	5000
d[13]	0.6217	0.2782	0.008488	0.09102	0.6165	1.194	50001	5000
d[14]	1.202	0.2302	0.008453	0.7564	1.2	1.667	50001	5000
or[1,2]	0.4107	0.07978	0.001746	0.2779	0.4029	0.5916	50001	5000
or[1,3]	0.3171	0.08641	0.003069	0.1781	0.309	0.5075	50001	5000
or[1,4]	0.3536	0.06348	0.002347	0.2412	0.3486	0.4908	50001	5000
or[1,5]	0.1861	0.08501	0.002623	0.06825	0.1709	0.3954	50001	5000
or[1,6]	0.4104	0.1244	0.003053	0.2145	0.3938	0.704	50001	5000
or[1,7]	0.2999	0.06137	0.002257	0.1887	0.2966	0.433	50001	5000
or[1,8]	0.4837	0.122	0.003743	0.2787	0.4711	0.7515	50001	5000
or[1,9]	0.4774	0.1225	0.003379	0.2838	0.4628	0.7587	50001	5000
or[1,10]	0.7342	0.3754	0.006939	0.2674	0.667	1.6	50001	5000
or[1,11]	0.2859	0.08863	0.002711	0.1542	0.2734	0.4914	50001	5000
or[1,12]	0.4132	0.2282	0.009619	0.1588	0.3605	1.013	50001	5000
or[1,13]	0.558	0.1563	0.004771	0.3033	0.5399	0.9146	50001	5000
or[1,14]	0.3087	0.07165	0.002561	0.1891	0.3013	0.4694	50001	5000
or[2,1]	2.527	0.4929	0.01111	1.692	2.483	3.599	50001	5000
or[2,2]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[2,3]	0.7985	0.2637	0.007936	0.3947	0.7568	1.417	50001	5000
or[2,4]	0.8887	0.2173	0.005923	0.5373	0.8614	1.39	50001	5000
or[2,5]	0.4699	0.2374	0.006563	0.1602	0.4235	1.076	50001	5000

or[2,6]	1.037	0.3772	0.00904	0.4744	0.975	1.946	50001	5000
or[2,7]	0.7558	0.2085	0.006392	0.4223	0.7321	1.239	50001	5000
or[2,8]	1.211	0.3508	0.009806	0.6492	1.172	2.017	50001	5000
or[2,9]	1.193	0.3377	0.008759	0.6598	1.15	1.954	50001	5000
or[2,10]	1.855	1.019	0.0183	0.6082	1.652	4.231	50001	5000
or[2,11]	0.7203	0.2607	0.007358	0.3401	0.678	1.341	50001	5000
or[2,12]	1.044	0.6237	0.02546	0.3598	0.9035	2.669	50001	5000
or[2,13]	1.403	0.4644	0.01297	0.7018	1.337	2.49	50001	5000
or[2,14]	0.7778	0.2281	0.006172	0.4194	0.7468	1.309	50001	5000
or[3,1]	3.393	0.9489	0.03265	1.971	3.237	5.616	50001	5000
or[3,2]	1.388	0.4632	0.0145	0.7068	1.321	2.534	50001	5000
or[3,3]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[3,4]	1.189	0.3607	0.01263	0.6474	1.142	2.01	50001	5000
or[3,5]	0.6321	0.3542	0.01034	0.1933	0.5518	1.558	50001	5000
or[3,6]	1.393	0.589	0.01761	0.5745	1.285	2.834	50001	5000
or[3,7]	1.013	0.3406	0.01221	0.5044	0.9566	1.854	50001	5000
or[3,8]	1.635	0.6102	0.01852	0.7315	1.534	3.121	50001	5000
or[3,9]	1.612	0.5991	0.01972	0.7551	1.507	3.099	50001	5000
or[3,10]	2.483	1.45	0.02967	0.762	2.195	5.918	50001	5000
or[3,11]	0.965	0.3987	0.012	0.4189	0.8921	1.94	50001	5000
or[3,12]	1.398	0.8712	0.03537	0.456	1.177	3.648	50001	5000
or[3,13]	1.872	0.7018	0.02272	0.885	1.745	3.534	50001	5000
or[3,14]	1.037	0.3468	0.01144	0.5139	0.9821	1.84	50001	5000
or[4,1]	2.919	0.5273	0.01958	2.038	2.869	4.147	50001	5000
or[4,2]	1.192	0.2909	0.007924	0.7213	1.161	1.862	50001	5000
or[4,3]	0.918	0.279	0.009932	0.4985	0.876	1.546	50001	5000
or[4,4]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[4,5]	0.5406	0.2626	0.008061	0.1915	0.4879	1.182	50001	5000
or[4,6]	1.194	0.4135	0.01059	0.5746	1.133	2.19	50001	5000
or[4,7]	0.8661	0.2015	0.007501	0.5302	0.8462	1.334	50001	5000
or[4,8]	1.398	0.3899	0.01264	0.7829	1.339	2.297	50001	5000
or[4,9]	1.39	0.4264	0.01383	0.7506	1.327	2.418	50001	5000
or[4,10]	2.142	1.163	0.02307	0.73	1.919	4.846	50001	5000
or[4,11]	0.8228	0.2601	0.007328	0.4335	0.7845	1.434	50001	5000
or[4,12]	1.19	0.649	0.02738	0.4413	1.043	2.855	50001	5000
or[4,13]	1.622	0.526	0.01662	0.8185	1.556	2.871	50001	5000
or[4,14]	0.8858	0.2016	0.006694	0.5573	0.8596	1.336	50001	5000
or[5,1]	6.531	3.288	0.1157	2.536	5.852	14.66	50001	5000
or[5,2]	2.677	1.456	0.04636	0.9294	2.362	6.308	50001	5000
or[5,3]	2.07	1.221	0.03897	0.6437	1.812	5.204	50001	5000
or[5,4]	2.295	1.197	0.03874	0.848	2.05	5.231	50001	5000
or[5,5]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[5,6]	2.672	1.621	0.04912	0.8174	2.316	6.636	50001	5000
or[5,7]	1.955	1.066	0.03516	0.6719	1.717	4.553	50001	5000
or[5,8]	3.15	1.794	0.05298	1.026	2.755	7.529	50001	5000
or[5,9]	3.11	1.795	0.05865	1.037	2.723	7.501	50001	5000
or[5,10]	4.801	3.679	0.1041	1.181	3.869	13.77	50001	5000
or[5,11]	1.851	1.08	0.03124	0.5856	1.612	4.51	50001	5000
or[5,12]	2.688	2.076	0.07465	0.6582	2.121	8.163	50001	5000
or[5,13]	3.622	2.123	0.06779	1.202	3.129	8.84	50001	5000
or[5,14]	2.012	1.125	0.03638	0.6848	1.772	4.766	50001	5000
or[6,1]	2.664	0.8302	0.02023	1.421	2.54	4.664	50001	5000
or[6,2]	1.094	0.4074	0.009772	0.5144	1.026	2.118	50001	5000
or[6,3]	0.8444	0.3539	0.0103	0.3536	0.7785	1.742	50001	5000
or[6,4]	0.9382	0.3281	0.007893	0.4569	0.8826	1.742	50001	5000
or[6,5]	0.4947	0.2848	0.007716	0.1509	0.4319	1.228	50001	5000
or[6,6]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[6,7]	0.789	0.2674	0.007402	0.392	0.7476	1.431	50001	5000
or[6,8]	1.287	0.5236	0.01269	0.5518	1.193	2.541	50001	5000
or[6,9]	1.273	0.5417	0.01404	0.5703	1.167	2.605	50001	5000
or[6,10]	1.949	1.22	0.02262	0.5963	1.715	4.644	50001	5000
or[6,11]	0.7575	0.3323	0.009191	0.3127	0.6934	1.566	50001	5000

or[6,12]	1.095	0.7089	0.02537	0.3425	0.9217	2.939	50001	5000
or[6,13]	1.485	0.6386	0.01708	0.6241	1.355	3.133	50001	5000
or[6,14]	0.818	0.3116	0.008111	0.3773	0.7668	1.595	50001	5000
or[7,1]	3.482	0.7557	0.02785	2.313	3.372	5.3	50001	5000
or[7,2]	1.426	0.4009	0.01212	0.8085	1.366	2.369	50001	5000
or[7,3]	1.098	0.3688	0.01338	0.5396	1.045	1.984	50001	5000
or[7,4]	1.217	0.2859	0.0103	0.7494	1.182	1.887	50001	5000
or[7,5]	0.647	0.3291	0.009561	0.2199	0.5826	1.49	50001	5000
or[7,6]	1.411	0.4764	0.01345	0.7015	1.338	2.553	50001	5000
or[7,7]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[7,8]	1.674	0.5254	0.01659	0.8696	1.597	2.905	50001	5000
or[7,9]	1.661	0.5657	0.01858	0.8533	1.575	3.051	50001	5000
or[7,10]	2.553	1.428	0.03081	0.8536	2.273	5.905	50001	5000
or[7,11]	0.9766	0.3159	0.01037	0.508	0.9282	1.727	50001	5000
or[7,12]	1.423	0.8003	0.03107	0.5094	1.232	3.579	50001	5000
or[7,13]	1.934	0.665	0.01738	0.9433	1.829	3.519	50001	5000
or[7,14]	1.06	0.2863	0.009835	0.6117	1.019	1.733	50001	5000
or[8,1]	2.204	0.5772	0.01709	1.332	2.123	3.592	50001	5000
or[8,2]	0.8973	0.2697	0.007155	0.4966	0.8536	1.544	50001	5000
or[8,3]	0.6965	0.262	0.008014	0.322	0.6517	1.368	50001	5000
or[8,4]	0.7711	0.2161	0.006836	0.4358	0.7467	1.278	50001	5000
or[8,5]	0.4094	0.2198	0.005581	0.1328	0.3629	0.9753	50001	5000
or[8,6]	0.9033	0.3641	0.008663	0.3937	0.8381	1.813	50001	5000
or[8,7]	0.6574	0.2102	0.006771	0.3444	0.6262	1.151	50001	5000
or[8,8]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[8,9]	1.05	0.3833	0.01143	0.5071	0.9863	1.984	50001	5000
or[8,10]	1.615	0.9471	0.01815	0.5219	1.422	3.789	50001	5000
or[8,11]	0.6274	0.2537	0.00778	0.2803	0.5797	1.24	50001	5000
or[8,12]	0.9054	0.5685	0.02015	0.3116	0.7661	2.349	50001	5000
or[8,13]	1.228	0.4812	0.01452	0.5566	1.135	2.364	50001	5000
or[8,14]	0.6759	0.2259	0.00673	0.3414	0.6409	1.227	50001	5000
or[9,1]	2.231	0.5692	0.01642	1.319	2.161	3.525	50001	5000
or[9,2]	0.9062	0.2606	0.007071	0.5122	0.8695	1.517	50001	5000
or[9,3]	0.704	0.2577	0.008228	0.3233	0.6636	1.326	50001	5000
or[9,4]	0.7865	0.2391	0.008152	0.4155	0.7538	1.333	50001	5000
or[9,5]	0.4144	0.2211	0.006359	0.1334	0.3675	0.9641	50001	5000
or[9,6]	0.9146	0.3637	0.009147	0.384	0.8571	1.758	50001	5000
or[9,7]	0.6685	0.2209	0.008138	0.3281	0.6354	1.172	50001	5000
or[9,8]	1.076	0.3838	0.01124	0.5047	1.014	1.976	50001	5000
or[9,9]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[9,10]	1.641	0.9597	0.02114	0.5108	1.434	3.911	50001	5000
or[9,11]	0.6371	0.2566	0.008304	0.2724	0.5923	1.292	50001	5000
or[9,12]	0.9237	0.6074	0.02518	0.2976	0.7858	2.318	50001	5000
or[9,13]	1.244	0.4858	0.01515	0.5491	1.161	2.416	50001	5000
or[9,14]	0.6879	0.2382	0.007871	0.3344	0.6507	1.257	50001	5000
or[10,1]	1.664	0.8586	0.01569	0.6264	1.499	3.749	50001	5000
or[10,2]	0.6836	0.3811	0.006752	0.237	0.6054	1.657	50001	5000
or[10,3]	0.5274	0.3216	0.006715	0.169	0.4556	1.318	50001	5000
or[10,4]	0.5883	0.3268	0.006384	0.2064	0.5211	1.37	50001	5000
or[10,5]	0.3081	0.2156	0.005047	0.07301	0.2585	0.8507	50001	5000
or[10,6]	0.6783	0.3953	0.008176	0.2154	0.5832	1.683	50001	5000
or[10,7]	0.4985	0.2829	0.005705	0.1705	0.44	1.176	50001	5000
or[10,8]	0.8022	0.462	0.008587	0.264	0.7034	1.917	50001	5000
or[10,9]	0.7965	0.4792	0.01012	0.2557	0.698	1.959	50001	5000
or[10,10]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[10,11]	0.4751	0.2925	0.005487	0.1491	0.4092	1.201	50001	5000
or[10,12]	0.6889	0.5654	0.01655	0.1683	0.5466	2.14	50001	5000
or[10,13]	0.9306	0.5706	0.01091	0.2922	0.8073	2.271	50001	5000
or[10,14]	0.5118	0.2882	0.005148	0.1727	0.4544	1.236	50001	5000
or[11,1]	3.823	1.157	0.03686	2.035	3.658	6.489	50001	5000
or[11,2]	1.566	0.5627	0.01629	0.7472	1.475	2.942	50001	5000
or[11,3]	1.206	0.4829	0.01596	0.5155	1.121	2.388	50001	5000

or[11,4]	1.333	0.4115	0.0127	0.6975	1.275	2.31	50001	5000
or[11,5]	0.7085	0.4024	0.01146	0.2226	0.6203	1.712	50001	5000
or[11,6]	1.56	0.6583	0.01923	0.6386	1.442	3.207	50001	5000
or[11,7]	1.125	0.3488	0.01153	0.5795	1.078	1.969	50001	5000
or[11,8]	1.841	0.7114	0.02138	0.8076	1.726	3.575	50001	5000
or[11,9]	1.825	0.7421	0.02217	0.7768	1.689	3.682	50001	5000
or[11,10]	2.807	1.726	0.03829	0.8325	2.444	6.721	50001	5000
or[11,11]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[11,12]	1.569	1.0	0.03958	0.4864	1.325	4.072	50001	5000
or[11,13]	2.121	0.8682	0.02563	0.9066	1.971	4.26	50001	5000
or[11,14]	1.148	0.339	0.01027	0.6072	1.11	1.922	50001	5000
or[12,1]	3.002	1.347	0.05696	0.9965	2.774	6.314	50001	5000
or[12,2]	1.233	0.617	0.02324	0.3769	1.107	2.787	50001	5000
or[12,3]	0.9494	0.5025	0.01938	0.2742	0.85	2.193	50001	5000
or[12,4]	1.052	0.4949	0.0216	0.3509	0.9586	2.268	50001	5000
or[12,5]	0.5581	0.3784	0.01416	0.1234	0.4716	1.521	50001	5000
or[12,6]	1.228	0.6887	0.0251	0.3419	1.085	2.922	50001	5000
or[12,7]	0.8941	0.4358	0.01756	0.2797	0.8115	1.965	50001	5000
or[12,8]	1.442	0.7342	0.02749	0.4283	1.305	3.211	50001	5000
or[12,9]	1.435	0.7677	0.02954	0.4343	1.273	3.367	50001	5000
or[12,10]	2.208	1.646	0.04919	0.4683	1.83	5.988	50001	5000
or[12,11]	0.8539	0.4768	0.01929	0.2462	0.7546	2.066	50001	5000
or[12,12]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[12,13]	1.666	0.888	0.0304	0.4791	1.496	3.9	50001	5000
or[12,14]	0.9191	0.4596	0.01937	0.2843	0.8234	2.085	50001	5000
or[13,1]	1.937	0.5627	0.01684	1.095	1.852	3.301	50001	5000
or[13,2]	0.7908	0.2642	0.006907	0.402	0.7482	1.426	50001	5000
or[13,3]	0.6063	0.22	0.00689	0.2831	0.5731	1.134	50001	5000
or[13,4]	0.6818	0.2255	0.007283	0.3488	0.6429	1.224	50001	5000
or[13,5]	0.3578	0.1932	0.005586	0.1133	0.3196	0.8332	50001	5000
or[13,6]	0.7931	0.3321	0.008216	0.3198	0.7383	1.61	50001	5000
or[13,7]	0.5785	0.2018	0.005565	0.2843	0.547	1.061	50001	5000
or[13,8]	0.9342	0.3532	0.01031	0.4232	0.8808	1.804	50001	5000
or[13,9]	0.923	0.358	0.0105	0.4142	0.8613	1.823	50001	5000
or[13,10]	1.425	0.8753	0.01622	0.4407	1.239	3.434	50001	5000
or[13,11]	0.55	0.2271	0.006472	0.2353	0.5074	1.106	50001	5000
or[13,12]	0.7932	0.4827	0.01752	0.2565	0.6683	2.088	50001	5000
or[13,13]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[13,14]	0.5942	0.2104	0.005893	0.2814	0.5593	1.11	50001	5000
or[14,1]	3.415	0.8001	0.02964	2.131	3.319	5.296	50001	5000
or[14,2]	1.399	0.4212	0.01226	0.7642	1.339	2.387	50001	5000
or[14,3]	1.073	0.3607	0.01288	0.5439	1.018	1.948	50001	5000
or[14,4]	1.187	0.2673	0.008836	0.7488	1.163	1.794	50001	5000
or[14,5]	0.6355	0.3385	0.01012	0.2099	0.5646	1.461	50001	5000
or[14,6]	1.394	0.5189	0.01313	0.6273	1.304	2.652	50001	5000
or[14,7]	1.011	0.2683	0.009559	0.5773	0.9814	1.635	50001	5000
or[14,8]	1.641	0.5367	0.01665	0.8154	1.561	2.93	50001	5000
or[14,9]	1.629	0.5675	0.0181	0.7982	1.537	2.996	50001	5000
or[14,10]	2.501	1.404	0.0271	0.8112	2.201	5.796	50001	5000
or[14,11]	0.9504	0.298	0.009145	0.5211	0.9005	1.651	50001	5000
or[14,12]	1.393	0.7883	0.03157	0.4801	1.214	3.526	50001	5000
or[14,13]	1.896	0.6794	0.02013	0.9021	1.788	3.557	50001	5000
or[14,14]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000

```
# Model - heterogeneous random effects model
# Assume correlation within study (rho = 0.5)
# Assume heterogeneous between studies ;"sdmu" is  (0.01, 5)



model {
  for (i in 1:NS) {
    s[i,1] <- 0
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(mmu[t[i,1]], taumu)  # handle different baseline treatments

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau[t[i,1],t[i,k]]*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  mmu[5] <- 0    #Treatments 1,2,3,4,6,7 are one of baseline treatments.
  mmu[8] <- 0    # other treatments should be assigned to 0.
  mmu[9] <- 0
  mmu[10] <- 0
  mmu[11] <- 0
mmu[12] <- 0
mmu[13] <- 0
mmu[14] <- 0
  mmu[1] ~ dnorm(0, 0.0001)
  mmu[2] ~ dnorm(0, 0.0001)
  mmu[3] ~ dnorm(0, 0.0001)
  mmu[4] ~ dnorm(0, 0.0001)
  mmu[6] ~ dnorm(0, 0.0001)
  mmu[7] ~ dnorm(0, 0.0001)
  sdmu ~ dunif(0.01, 5)
  taumu <- 1/pow(sdmu,2)

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0,0.0001)
    ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

  for(i in 1:(NT-1)) {
    for(j in (i+1):NT) {
      v[i,j] ~ dnorm(0, 8.32)
      log(sd[i,j]) <- log(sd0) + v[i,j]
      tau[i,j] <- 1/pow(sd[i,j],2)
      var[i,j] <- pow(sd[i,j],2)
    }
  }
  sd0 ~ dunif(0.01, 2)
  var0 <- pow(sd0,2)
```

```
  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mmu[1]  # "mP" means the odds of placebo.

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0,    0,0,0,0),
sd0=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,    0,0,0,0,0,  0,0),
mmu=c(0,0,0,0,NA, 0,0,NA,NA,NA, NA,NA,NA,NA), sdmu=1
)


#Data


#Data
list(NT=14, NS=97)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
17	83	34	83	NA	1	1	4	NA	2
18	61	26	55	NA	1	1	8	NA	2
0	14	2	14	NA	1	1	7	NA	2
15	22	14	22	NA	1	3	14	NA	2
24	48	31	46	NA	1	4	14	NA	2
1	16	6	16	NA	1	1	8	NA	2
45	75	44	74	NA	1	7	14	NA	2
818	11034	661	11037	NA	1	1	6	NA	2
3	28	14	28	NA	1	6	7	NA	2
12	20	6	20	NA	1	4	12	NA	2
5	44	18	47	NA	1	4	7	NA	2
16	77	29	77	NA	1	1	7	NA	2
9	15	5	13	NA	1	4	7	NA	2
12	54	10	54	NA	1	4	8	NA	2
10	31	8	31	NA	1	7	11	NA	2
5	19	6	19	NA	1	1	6	NA	2

5	48	26	48	NA	1	1	9	NA	2
4	18	10	17	NA	1	1	14	NA	2
12	48	48	96	NA	1	1	4	NA	2
10	47	25	47	NA	1	1	4	NA	2
15	36	17	36	NA	1	4	7	NA	2
3	15	1	14	NA	1	4	8	NA	2
4	37	10	34	NA	1	1	7	NA	2
3	13	13	25	NA	1	1	4	NA	2
13	23	8	23	NA	1	4	11	NA	2
5	37	33	70	NA	1	1	3	NA	2
6	43	17	43	NA	1	1	3	NA	2
7	23	16	23	NA	1	1	6	NA	2
7	32	14	36	NA	1	1	13	NA	2
10	34	10	35	NA	1	1	13	NA	2
2	15	19	44	NA	1	1	3	NA	2
24	37	25	37	NA	1	3	4	NA	2
0	60	14	60	NA	1	1	5	NA	2
5	45	26	98	NA	1	1	9	NA	2
34	69	32	66	NA	1	11	14	NA	2
61	135	40	135	NA	1	6	7	NA	2
2	21	5	19	NA	1	1	2	NA	2
9	27	8	26	NA	1	1	9	NA	2
125	270	141	275	NA	1	4	14	NA	2
32	116	50	123	NA	1	1	3	NA	2
2	60	23	60	NA	1	1	5	NA	2
1	14	10	14	NA	1	1	2	NA	2
18	84	23	93	NA	1	1	13	NA	2
112	200	112	184	NA	1	1	10	NA	2
12	57	37	58	NA	1	1	2	NA	2
0	19	9	21	NA	1	1	8	NA	2
93	372	188	386	NA	1	1	2	NA	2
20	22	21	22	NA	1	2	3	NA	2
25	73	55	140	NA	1	1	2	NA	2
16	372	8	384	NA	1	1	2	NA	2
0	27	7	32	NA	1	1	2	NA	2
8	13	8	15	NA	1	2	9	NA	2
27	45	30	45	NA	1	2	13	NA	2
31	85	28	85	NA	1	1	9	NA	2
37	58	41	67	NA	1	3	13	NA	2
24	65	24	59	NA	1	1	13	NA	2
99	178	78	169	NA	1	2	8	NA	2

50	163	64	165	NA	1	1	2	NA	2
11	25	7	24	NA	1	4	8	NA	2
6	16	18	53	NA	1	1	4	NA	2
48	197	47	194	NA	1	1	8	NA	2
16	40	15	40	NA	1	2	9	NA	2
8	84	20	91	NA	1	1	6	NA	2
0	11	5	8	NA	1	1	4	NA	2
0	28	3	28	NA	1	1	7	NA	2
2	43	13	43	NA	1	1	7	NA	2
2	31	14	31	NA	1	1	6	NA	2
0	8	6	24	NA	1	1	7	NA	2
0	33	10	33	NA	1	1	12	NA	2
8	34	12	35	NA	1	4	14	NA	2
2	29	8	29	NA	1	1	14	NA	2
17	71	20	72	NA	1	1	14	NA	2
4	36	20	36	NA	1	1	12	NA	2
0	17	5	17	NA	1	4	14	NA	2
4	30	8	30	NA	1	1	12	NA	2
19	75	28	75	NA	1	1	10	NA	2
24	54	14	48	NA	1	11	14	NA	2
7	36	16	37	NA	1	1	8	NA	2
12	33	11	33	NA	1	1	7	NA	2
1	13	3	11	NA	1	4	8	NA	2
0	29	5	29	NA	1	1	14	NA	2
1	40	17	40	NA	1	1	6	NA	2
0	12	8	12	NA	1	1	5	NA	2
1	14	2	14	NA	1	4	13	NA	2
0	30	10	30	NA	1	1	11	NA	2
11	35	10	38	NA	1	1	6	NA	2
6	14	6	18	NA	1	11	14	NA	2
12	22	18	23	NA	1	1	9	NA	2
16	32	13	27	NA	1	4	14	NA	2
11	47	16	48	NA	1	1	5	NA	2
0	24	8	24	NA	1	1	7	NA	2
10	20	40	62	NA	1	1	9	NA	2
8	36	58	112	NA	1	1	2	NA	2
0	19	6	22	0	17	4	7	12	3
11	49	50	144	62	144	1	2	4	3
18	60	38	60	28	60	1	2	9	3
13	50	21	50	22	50	1	7	11	3

END

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
best1[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[2]	0.0018	0.04239	7.992E-4	0.0	0.0	0.0	50001	5000
best1[3]	0.053	0.224	0.004245	0.0	0.0	1.0	50001	5000
best1[4]	0.0014	0.03739	5.815E-4	0.0	0.0	0.0	50001	5000
best1[5]	0.7118	0.4529	0.01115	0.0	1.0	1.0	50001	5000
best1[6]	0.01	0.0995	0.001563	0.0	0.0	0.0	50001	5000
best1[7]	0.027	0.1621	0.002892	0.0	0.0	1.0	50001	5000
best1[8]	0.0018	0.04239	5.62E-4	0.0	0.0	0.0	50001	5000
best1[9]	0.0016	0.03997	6.033E-4	0.0	0.0	0.0	50001	5000
best1[10]	0.0048	0.06912	0.001058	0.0	0.0	0.0	50001	5000
best1[11]	0.1004	0.3005	0.006587	0.0	0.0	1.0	50001	5000
best1[12]	0.0584	0.2345	0.007058	0.0	0.0	1.0	50001	5000
best1[13]	4.0E-4	0.02	2.817E-4	0.0	0.0	0.0	50001	5000
best1[14]	0.0276	0.1638	0.003541	0.0	0.0	1.0	50001	5000
best2[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[2]	0.0096	0.09751	0.001736	0.0	0.0	0.0	50001	5000
best2[3]	0.1468	0.3539	0.007527	0.0	0.0	1.0	50001	5000
best2[4]	0.0162	0.1262	0.002781	0.0	0.0	0.0	50001	5000
best2[5]	0.117	0.3214	0.005758	0.0	0.0	1.0	50001	5000
best2[6]	0.0454	0.2082	0.003424	0.0	0.0	1.0	50001	5000
best2[7]	0.149	0.3561	0.009166	0.0	0.0	1.0	50001	5000
best2[8]	0.0074	0.0857	0.001582	0.0	0.0	0.0	50001	5000
best2[9]	0.008	0.08908	0.001439	0.0	0.0	0.0	50001	5000
best2[10]	0.011	0.1043	0.001426	0.0	0.0	0.0	50001	5000
best2[11]	0.2504	0.4332	0.009641	0.0	0.0	1.0	50001	5000
best2[12]	0.12	0.325	0.008177	0.0	0.0	1.0	50001	5000
best2[13]	0.0028	0.05284	0.001012	0.0	0.0	0.0	50001	5000
best2[14]	0.1164	0.3207	0.006902	0.0	0.0	1.0	50001	5000
d[2]	0.9084	0.1925	0.004303	0.5261	0.9094	1.281	50001	5000
d[3]	1.185	0.2705	0.009589	0.6785	1.175	1.726	50001	5000
d[4]	1.055	0.1783	0.006629	0.712	1.054	1.422	50001	5000
d[5]	1.776	0.4397	0.01533	0.9306	1.767	2.685	50001	5000
d[6]	0.9348	0.2981	0.007378	0.3516	0.9321	1.54	50001	5000
d[7]	1.226	0.2077	0.007711	0.8384	1.216	1.668	50001	5000
d[8]	0.7579	0.2531	0.007698	0.2864	0.7527	1.279	50001	5000
d[9]	0.7709	0.2503	0.007164	0.2765	0.7705	1.26	50001	5000
d[10]	0.4083	0.4418	0.008455	-0.4678	0.4051	1.321	50001	5000
d[11]	1.297	0.2976	0.009451	0.7107	1.297	1.87	50001	5000
d[12]	0.9983	0.4622	0.01963	-0.003467	1.02	1.843	50001	5000
d[13]	0.6217	0.2782	0.008488	0.09102	0.6165	1.194	50001	5000
d[14]	1.202	0.2302	0.008453	0.7564	1.2	1.667	50001	5000
or[1,2]	0.4107	0.07978	0.001746	0.2779	0.4029	0.5916	50001	5000
or[1,3]	0.3171	0.08641	0.003069	0.1781	0.309	0.5075	50001	5000
or[1,4]	0.3536	0.06348	0.002347	0.2412	0.3486	0.4908	50001	5000
or[1,5]	0.1861	0.08501	0.002623	0.06825	0.1709	0.3954	50001	5000
or[1,6]	0.4104	0.1244	0.003053	0.2145	0.3938	0.704	50001	5000
or[1,7]	0.2999	0.06137	0.002257	0.1887	0.2966	0.433	50001	5000
or[1,8]	0.4837	0.122	0.003743	0.2787	0.4711	0.7515	50001	5000
or[1,9]	0.4774	0.1225	0.003379	0.2838	0.4628	0.7587	50001	5000
or[1,10]	0.7342	0.3754	0.006939	0.2674	0.667	1.6	50001	5000
or[1,11]	0.2859	0.08863	0.002711	0.1542	0.2734	0.4914	50001	5000
or[1,12]	0.4132	0.2282	0.009619	0.1588	0.3605	1.013	50001	5000
or[1,13]	0.558	0.1563	0.004771	0.3033	0.5399	0.9146	50001	5000
or[1,14]	0.3087	0.07165	0.002561	0.1891	0.3013	0.4694	50001	5000
or[2,1]	2.527	0.4929	0.01111	1.692	2.483	3.599	50001	5000
or[2,2]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[2,3]	0.7985	0.2637	0.007936	0.3947	0.7568	1.417	50001	5000
or[2,4]	0.8887	0.2173	0.005923	0.5373	0.8614	1.39	50001	5000
or[2,5]	0.4699	0.2374	0.006563	0.1602	0.4235	1.076	50001	5000

or[2,6]	1.037	0.3772	0.00904	0.4744	0.975	1.946	50001	5000
or[2,7]	0.7558	0.2085	0.006392	0.4223	0.7321	1.239	50001	5000
or[2,8]	1.211	0.3508	0.009806	0.6492	1.172	2.017	50001	5000
or[2,9]	1.193	0.3377	0.008759	0.6598	1.15	1.954	50001	5000
or[2,10]	1.855	1.019	0.0183	0.6082	1.652	4.231	50001	5000
or[2,11]	0.7203	0.2607	0.007358	0.3401	0.678	1.341	50001	5000
or[2,12]	1.044	0.6237	0.02546	0.3598	0.9035	2.669	50001	5000
or[2,13]	1.403	0.4644	0.01297	0.7018	1.337	2.49	50001	5000
or[2,14]	0.7778	0.2281	0.006172	0.4194	0.7468	1.309	50001	5000
or[3,1]	3.393	0.9489	0.03265	1.971	3.237	5.616	50001	5000
or[3,2]	1.388	0.4632	0.0145	0.7068	1.321	2.534	50001	5000
or[3,3]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[3,4]	1.189	0.3607	0.01263	0.6474	1.142	2.01	50001	5000
or[3,5]	0.6321	0.3542	0.01034	0.1933	0.5518	1.558	50001	5000
or[3,6]	1.393	0.589	0.01761	0.5745	1.285	2.834	50001	5000
or[3,7]	1.013	0.3406	0.01221	0.5044	0.9566	1.854	50001	5000
or[3,8]	1.635	0.6102	0.01852	0.7315	1.534	3.121	50001	5000
or[3,9]	1.612	0.5991	0.01972	0.7551	1.507	3.099	50001	5000
or[3,10]	2.483	1.45	0.02967	0.762	2.195	5.918	50001	5000
or[3,11]	0.965	0.3987	0.012	0.4189	0.8921	1.94	50001	5000
or[3,12]	1.398	0.8712	0.03537	0.456	1.177	3.648	50001	5000
or[3,13]	1.872	0.7018	0.02272	0.885	1.745	3.534	50001	5000
or[3,14]	1.037	0.3468	0.01144	0.5139	0.9821	1.84	50001	5000
or[4,1]	2.919	0.5273	0.01958	2.038	2.869	4.147	50001	5000
or[4,2]	1.192	0.2909	0.007924	0.7213	1.161	1.862	50001	5000
or[4,3]	0.918	0.279	0.009932	0.4985	0.876	1.546	50001	5000
or[4,4]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[4,5]	0.5406	0.2626	0.008061	0.1915	0.4879	1.182	50001	5000
or[4,6]	1.194	0.4135	0.01059	0.5746	1.133	2.19	50001	5000
or[4,7]	0.8661	0.2015	0.007501	0.5302	0.8462	1.334	50001	5000
or[4,8]	1.398	0.3899	0.01264	0.7829	1.339	2.297	50001	5000
or[4,9]	1.39	0.4264	0.01383	0.7506	1.327	2.418	50001	5000
or[4,10]	2.142	1.163	0.02307	0.73	1.919	4.846	50001	5000
or[4,11]	0.8228	0.2601	0.007328	0.4335	0.7845	1.434	50001	5000
or[4,12]	1.19	0.649	0.02738	0.4413	1.043	2.855	50001	5000
or[4,13]	1.622	0.526	0.01662	0.8185	1.556	2.871	50001	5000
or[4,14]	0.8858	0.2016	0.006694	0.5573	0.8596	1.336	50001	5000
or[5,1]	6.531	3.288	0.1157	2.536	5.852	14.66	50001	5000
or[5,2]	2.677	1.456	0.04636	0.9294	2.362	6.308	50001	5000
or[5,3]	2.07	1.221	0.03897	0.6437	1.812	5.204	50001	5000
or[5,4]	2.295	1.197	0.03874	0.848	2.05	5.231	50001	5000
or[5,5]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[5,6]	2.672	1.621	0.04912	0.8174	2.316	6.636	50001	5000
or[5,7]	1.955	1.066	0.03516	0.6719	1.717	4.553	50001	5000
or[5,8]	3.15	1.794	0.05298	1.026	2.755	7.529	50001	5000
or[5,9]	3.11	1.795	0.05865	1.037	2.723	7.501	50001	5000
or[5,10]	4.801	3.679	0.1041	1.181	3.869	13.77	50001	5000
or[5,11]	1.851	1.08	0.03124	0.5856	1.612	4.51	50001	5000
or[5,12]	2.688	2.076	0.07465	0.6582	2.121	8.163	50001	5000
or[5,13]	3.622	2.123	0.06779	1.202	3.129	8.84	50001	5000
or[5,14]	2.012	1.125	0.03638	0.6848	1.772	4.766	50001	5000
or[6,1]	2.664	0.8302	0.02023	1.421	2.54	4.664	50001	5000
or[6,2]	1.094	0.4074	0.009772	0.5144	1.026	2.118	50001	5000
or[6,3]	0.8444	0.3539	0.0103	0.3536	0.7785	1.742	50001	5000
or[6,4]	0.9382	0.3281	0.007893	0.4569	0.8826	1.742	50001	5000
or[6,5]	0.4947	0.2848	0.007716	0.1509	0.4319	1.228	50001	5000
or[6,6]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[6,7]	0.789	0.2674	0.007402	0.392	0.7476	1.431	50001	5000
or[6,8]	1.287	0.5236	0.01269	0.5518	1.193	2.541	50001	5000
or[6,9]	1.273	0.5417	0.01404	0.5703	1.167	2.605	50001	5000
or[6,10]	1.949	1.22	0.02262	0.5963	1.715	4.644	50001	5000
or[6,11]	0.7575	0.3323	0.009191	0.3127	0.6934	1.566	50001	5000

or[6,12]	1.095	0.7089	0.02537	0.3425	0.9217	2.939	50001	5000
or[6,13]	1.485	0.6386	0.01708	0.6241	1.355	3.133	50001	5000
or[6,14]	0.818	0.3116	0.008111	0.3773	0.7668	1.595	50001	5000
or[7,1]	3.482	0.7557	0.02785	2.313	3.372	5.3	50001	5000
or[7,2]	1.426	0.4009	0.01212	0.8085	1.366	2.369	50001	5000
or[7,3]	1.098	0.3688	0.01338	0.5396	1.045	1.984	50001	5000
or[7,4]	1.217	0.2859	0.0103	0.7494	1.182	1.887	50001	5000
or[7,5]	0.647	0.3291	0.009561	0.2199	0.5826	1.49	50001	5000
or[7,6]	1.411	0.4764	0.01345	0.7015	1.338	2.553	50001	5000
or[7,7]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[7,8]	1.674	0.5254	0.01659	0.8696	1.597	2.905	50001	5000
or[7,9]	1.661	0.5657	0.01858	0.8533	1.575	3.051	50001	5000
or[7,10]	2.553	1.428	0.03081	0.8536	2.273	5.905	50001	5000
or[7,11]	0.9766	0.3159	0.01037	0.508	0.9282	1.727	50001	5000
or[7,12]	1.423	0.8003	0.03107	0.5094	1.232	3.579	50001	5000
or[7,13]	1.934	0.665	0.01738	0.9433	1.829	3.519	50001	5000
or[7,14]	1.06	0.2863	0.009835	0.6117	1.019	1.733	50001	5000
or[8,1]	2.204	0.5772	0.01709	1.332	2.123	3.592	50001	5000
or[8,2]	0.8973	0.2697	0.007155	0.4966	0.8536	1.544	50001	5000
or[8,3]	0.6965	0.262	0.008014	0.322	0.6517	1.368	50001	5000
or[8,4]	0.7711	0.2161	0.006836	0.4358	0.7467	1.278	50001	5000
or[8,5]	0.4094	0.2198	0.005581	0.1328	0.3629	0.9753	50001	5000
or[8,6]	0.9033	0.3641	0.008663	0.3937	0.8381	1.813	50001	5000
or[8,7]	0.6574	0.2102	0.006771	0.3444	0.6262	1.151	50001	5000
or[8,8]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[8,9]	1.05	0.3833	0.01143	0.5071	0.9863	1.984	50001	5000
or[8,10]	1.615	0.9471	0.01815	0.5219	1.422	3.789	50001	5000
or[8,11]	0.6274	0.2537	0.00778	0.2803	0.5797	1.24	50001	5000
or[8,12]	0.9054	0.5685	0.02015	0.3116	0.7661	2.349	50001	5000
or[8,13]	1.228	0.4812	0.01452	0.5566	1.135	2.364	50001	5000
or[8,14]	0.6759	0.2259	0.00673	0.3414	0.6409	1.227	50001	5000
or[9,1]	2.231	0.5692	0.01642	1.319	2.161	3.525	50001	5000
or[9,2]	0.9062	0.2606	0.007071	0.5122	0.8695	1.517	50001	5000
or[9,3]	0.704	0.2577	0.008228	0.3233	0.6636	1.326	50001	5000
or[9,4]	0.7865	0.2391	0.008152	0.4155	0.7538	1.333	50001	5000
or[9,5]	0.4144	0.2211	0.006359	0.1334	0.3675	0.9641	50001	5000
or[9,6]	0.9146	0.3637	0.009147	0.384	0.8571	1.758	50001	5000
or[9,7]	0.6685	0.2209	0.008138	0.3281	0.6354	1.172	50001	5000
or[9,8]	1.076	0.3838	0.01124	0.5047	1.014	1.976	50001	5000
or[9,9]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[9,10]	1.641	0.9597	0.02114	0.5108	1.434	3.911	50001	5000
or[9,11]	0.6371	0.2566	0.008304	0.2724	0.5923	1.292	50001	5000
or[9,12]	0.9237	0.6074	0.02518	0.2976	0.7858	2.318	50001	5000
or[9,13]	1.244	0.4858	0.01515	0.5491	1.161	2.416	50001	5000
or[9,14]	0.6879	0.2382	0.007871	0.3344	0.6507	1.257	50001	5000
or[10,1]	1.664	0.8586	0.01569	0.6264	1.499	3.749	50001	5000
or[10,2]	0.6836	0.3811	0.006752	0.237	0.6054	1.657	50001	5000
or[10,3]	0.5274	0.3216	0.006715	0.169	0.4556	1.318	50001	5000
or[10,4]	0.5883	0.3268	0.006384	0.2064	0.5211	1.37	50001	5000
or[10,5]	0.3081	0.2156	0.005047	0.07301	0.2585	0.8507	50001	5000
or[10,6]	0.6783	0.3953	0.008176	0.2154	0.5832	1.683	50001	5000
or[10,7]	0.4985	0.2829	0.005705	0.1705	0.44	1.176	50001	5000
or[10,8]	0.8022	0.462	0.008587	0.264	0.7034	1.917	50001	5000
or[10,9]	0.7965	0.4792	0.01012	0.2557	0.698	1.959	50001	5000
or[10,10]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[10,11]	0.4751	0.2925	0.005487	0.1491	0.4092	1.201	50001	5000
or[10,12]	0.6889	0.5654	0.01655	0.1683	0.5466	2.14	50001	5000
or[10,13]	0.9306	0.5706	0.01091	0.2922	0.8073	2.271	50001	5000
or[10,14]	0.5118	0.2882	0.005148	0.1727	0.4544	1.236	50001	5000
or[11,1]	3.823	1.157	0.03686	2.035	3.658	6.489	50001	5000
or[11,2]	1.566	0.5627	0.01629	0.7472	1.475	2.942	50001	5000
or[11,3]	1.206	0.4829	0.01596	0.5155	1.121	2.388	50001	5000

or[11,4]	1.333	0.4115	0.0127	0.6975	1.275	2.31	50001	5000
or[11,5]	0.7085	0.4024	0.01146	0.2226	0.6203	1.712	50001	5000
or[11,6]	1.56	0.6583	0.01923	0.6386	1.442	3.207	50001	5000
or[11,7]	1.125	0.3488	0.01153	0.5795	1.078	1.969	50001	5000
or[11,8]	1.841	0.7114	0.02138	0.8076	1.726	3.575	50001	5000
or[11,9]	1.825	0.7421	0.02217	0.7768	1.689	3.682	50001	5000
or[11,10]	2.807	1.726	0.03829	0.8325	2.444	6.721	50001	5000
or[11,11]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[11,12]	1.569	1.0	0.03958	0.4864	1.325	4.072	50001	5000
or[11,13]	2.121	0.8682	0.02563	0.9066	1.971	4.26	50001	5000
or[11,14]	1.148	0.339	0.01027	0.6072	1.11	1.922	50001	5000
or[12,1]	3.002	1.347	0.05696	0.9965	2.774	6.314	50001	5000
or[12,2]	1.233	0.617	0.02324	0.3769	1.107	2.787	50001	5000
or[12,3]	0.9494	0.5025	0.01938	0.2742	0.85	2.193	50001	5000
or[12,4]	1.052	0.4949	0.0216	0.3509	0.9586	2.268	50001	5000
or[12,5]	0.5581	0.3784	0.01416	0.1234	0.4716	1.521	50001	5000
or[12,6]	1.228	0.6887	0.0251	0.3419	1.085	2.922	50001	5000
or[12,7]	0.8941	0.4358	0.01756	0.2797	0.8115	1.965	50001	5000
or[12,8]	1.442	0.7342	0.02749	0.4283	1.305	3.211	50001	5000
or[12,9]	1.435	0.7677	0.02954	0.4343	1.273	3.367	50001	5000
or[12,10]	2.208	1.646	0.04919	0.4683	1.83	5.988	50001	5000
or[12,11]	0.8539	0.4768	0.01929	0.2462	0.7546	2.066	50001	5000
or[12,12]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[12,13]	1.666	0.888	0.0304	0.4791	1.496	3.9	50001	5000
or[12,14]	0.9191	0.4596	0.01937	0.2843	0.8234	2.085	50001	5000
or[13,1]	1.937	0.5627	0.01684	1.095	1.852	3.301	50001	5000
or[13,2]	0.7908	0.2642	0.006907	0.402	0.7482	1.426	50001	5000
or[13,3]	0.6063	0.22	0.00689	0.2831	0.5731	1.134	50001	5000
or[13,4]	0.6818	0.2255	0.007283	0.3488	0.6429	1.224	50001	5000
or[13,5]	0.3578	0.1932	0.005586	0.1133	0.3196	0.8332	50001	5000
or[13,6]	0.7931	0.3321	0.008216	0.3198	0.7383	1.61	50001	5000
or[13,7]	0.5785	0.2018	0.005565	0.2843	0.547	1.061	50001	5000
or[13,8]	0.9342	0.3532	0.01031	0.4232	0.8808	1.804	50001	5000
or[13,9]	0.923	0.358	0.0105	0.4142	0.8613	1.823	50001	5000
or[13,10]	1.425	0.8753	0.01622	0.4407	1.239	3.434	50001	5000
or[13,11]	0.55	0.2271	0.006472	0.2353	0.5074	1.106	50001	5000
or[13,12]	0.7932	0.4827	0.01752	0.2565	0.6683	2.088	50001	5000
or[13,13]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[13,14]	0.5942	0.2104	0.005893	0.2814	0.5593	1.11	50001	5000
or[14,1]	3.415	0.8001	0.02964	2.131	3.319	5.296	50001	5000
or[14,2]	1.399	0.4212	0.01226	0.7642	1.339	2.387	50001	5000
or[14,3]	1.073	0.3607	0.01288	0.5439	1.018	1.948	50001	5000
or[14,4]	1.187	0.2673	0.008836	0.7488	1.163	1.794	50001	5000
or[14,5]	0.6355	0.3385	0.01012	0.2099	0.5646	1.461	50001	5000
or[14,6]	1.394	0.5189	0.01313	0.6273	1.304	2.652	50001	5000
or[14,7]	1.011	0.2683	0.009559	0.5773	0.9814	1.635	50001	5000
or[14,8]	1.641	0.5367	0.01665	0.8154	1.561	2.93	50001	5000
or[14,9]	1.629	0.5675	0.0181	0.7982	1.537	2.996	50001	5000
or[14,10]	2.501	1.404	0.0271	0.8112	2.201	5.796	50001	5000
or[14,11]	0.9504	0.298	0.009145	0.5211	0.9005	1.651	50001	5000
or[14,12]	1.393	0.7883	0.03157	0.4801	1.214	3.526	50001	5000
or[14,13]	1.896	0.6794	0.02013	0.9021	1.788	3.557	50001	5000
or[14,14]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000

Outcome- treatment discontinuation due to intolerable adverse effects

```
# Model - heterogeneous random effects model
# Assume correlation within study (rho = 0.5)
# Assume heterogeneous between

model {
  for (i in 1:NS) {
    s[i,1] <- 0
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(mmu[t[i,1]], taumu)  # handle different baseline treatments

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau[t[i,1],t[i,k]]*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  mmu[5] <- 0    #Treatments 1,2,3,4,6,7 are one of baseline treatments.
  mmu[8] <- 0    # other treatments should be assigned to 0.
  mmu[9] <- 0
  mmu[10] <- 0
  mmu[11] <- 0
mmu[12] <- 0
mmu[13] <- 0
mmu[14] <- 0
  mmu[1] ~ dnorm(0, 0.0001)
  mmu[2] ~ dnorm(0, 0.0001)
  mmu[3] ~ dnorm(0, 0.0001)
  mmu[4] ~ dnorm(0, 0.0001)
  mmu[6] ~ dnorm(0, 0.0001)
  mmu[7] ~ dnorm(0, 0.0001)
  sdmu ~ dunif(0.01, 2)
  taumu <- 1/pow(sdmu,2)

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0,0.0001)
    ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

  for(i in 1:(NT-1)) {
    for(j in (i+1):NT) {
      v[i,j] ~ dnorm(0, 8.32)
      log(sd[i,j]) <- log(sd0) + v[i,j]
      tau[i,j] <- 1/pow(sd[i,j],2)
      var[i,j] <- pow(sd[i,j],2)
    }
  }
  sd0 ~ dunif(0.01, 2)
  var0 <- pow(sd0,2)

  # pairwise ORs
```

```
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mmu[1]  # "mP" means the odds of placebo.

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0,    0,0,0,0),
sd0=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0),
mmu=c(0,0,0,0,NA, 0,0,NA,NA,NA, NA,NA,NA,NA), sdmu=1
)


#Data


#Data
list(NT=14, NS=68)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	96	2	96	NA	1	1	12	NA	2
2	61	5	55	NA	1	1	8	NA	2
1	83	6	83	NA	1	1	5	NA	2
3	48	5	46	NA	1	5	14	NA	2
2	32	1	32	NA	1	1	3	NA	2
1	75	10	74	NA	1	7	14	NA	2
5	20	13	20	NA	1	5	9	NA	2
5	24	9	31	NA	1	1	5	NA	2
4	46	3	43	NA	1	1	9	NA	2
4	44	2	47	NA	1	5	7	NA	2
2	34	4	31	NA	1	1	8	NA	2
0	31	4	31	NA	1	7	12	NA	2
0	48	1	48	NA	1	1	4	NA	2
2	74	1	74	NA	1	1	10	NA	2
0	47	2	47	NA	1	1	6	NA	2
1	37	1	34	NA	1	1	7	NA	2
2	37	9	70	NA	1	1	3	NA	2

2	43	4	43	NA	1	1	3	NA	2
0	38	3	43	NA	1	1	13	NA	2
1	34	3	35	NA	1	1	13	NA	2
3	40	7	18	NA	1	1	4	NA	2
2	38	7	77	NA	1	1	7	NA	2
4	37	1	37	NA	1	3	5	NA	2
4	26	4	27	NA	1	1	8	NA	2
4	45	16	98	NA	1	1	4	NA	2
6	69	1	66	NA	1	13	14	NA	2
5	20	4	20	NA	1	5	10	NA	2
2	27	9	26	NA	1	1	4	NA	2
18	270	19	275	NA	1	5	14	NA	2
10	116	10	123	NA	1	1	3	NA	2
4	64	9	72	NA	1	1	13	NA	2
0	36	6	34	NA	1	1	2	NA	2
2	84	2	93	NA	1	1	13	NA	2
2	57	3	58	NA	1	1	2	NA	2
6	20	9	30	NA	1	1	2	NA	2
4	73	21	140	NA	1	1	2	NA	2
10	163	18	165	NA	1	1	2	NA	2
3	60	3	60	3	60	1	2	4	3
41	383	96	391	NA	1	1	2	NA	2
10	45	0	45	NA	1	2	13	NA	2
4	85	8	85	NA	1	1	4	NA	2
3	58	2	67	NA	1	3	13	NA	2
2	24	4	28	NA	1	2	8	NA	2
1	65	2	59	NA	1	1	13	NA	2
35	178	38	169	NA	1	2	8	NA	2
18	197	21	188	NA	1	1	2	NA	2
13	197	23	194	NA	1	1	8	NA	2
0	28	3	28	NA	1	1	7	NA	2
0	71	2	71	NA	1	1	12	NA	2
1	38	2	38	NA	1	1	11	NA	2
1	33	0	33	NA	1	1	9	NA	2
0	40	1	40	NA	1	1	11	NA	2
3	72	0	72	NA	1	1	7	NA	2
3	45	0	45	NA	1	1	10	NA	2
1	24	5	24	NA	1	1	9	NA	2
5	75	12	75	NA	1	1	10	NA	2
4	54	0	48	NA	1	13	14	NA	2
3	21	2	20	NA	1	8	10	NA	2

0	29	3	29	NA	1	5	8	NA	2
2	30	3	29	NA	1	1	8	NA	2
1	14	2	18	NA	1	9	14	NA	2
1	22	2	23	NA	1	1	4	NA	2
1	46	2	46	NA	1	1	11	NA	2
3	32	2	27	NA	1	5	14	NA	2
2	20	13	62	NA	1	1	4	NA	2
1	13	0	15	NA	1	2	4	NA	2
0	63	18	63	NA	1	7	8	NA	2
3	48	3	44	9	49	5	8	10	3

END

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
best1[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[2]	0.0516	0.2212	0.005231	0.0	0.0	1.0	50001	5000
best1[3]	0.0342	0.1817	0.005157	0.0	0.0	1.0	50001	5000
best1[4]	0.141	0.348	0.01226	0.0	0.0	1.0	50001	5000
best1[5]	4.0E-4	0.02	2.777E-4	0.0	0.0	0.0	50001	5000
best1[6]	0.3646	0.4813	0.02054	0.0	0.0	1.0	50001	5000
best1[7]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[8]	0.0412	0.1988	0.005382	0.0	0.0	1.0	50001	5000
best1[9]	0.086	0.2804	0.008756	0.0	0.0	1.0	50001	5000
best1[10]	0.0072	0.08455	0.001747	0.0	0.0	0.0	50001	5000
best1[11]	0.0628	0.2426	0.006461	0.0	0.0	1.0	50001	5000
best1[12]	0.1846	0.388	0.01594	0.0	0.0	1.0	50001	5000
best1[13]	0.0258	0.1585	0.004967	0.0	0.0	1.0	50001	5000
best1[14]	6.0E-4	0.02449	3.425E-4	0.0	0.0	0.0	50001	5000
best2[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[2]	0.1248	0.3305	0.0074	0.0	0.0	1.0	50001	5000
best2[3]	0.0636	0.244	0.006352	0.0	0.0	1.0	50001	5000
best2[4]	0.217	0.4122	0.009941	0.0	0.0	1.0	50001	5000
best2[5]	0.0018	0.04239	7.449E-4	0.0	0.0	0.0	50001	5000
best2[6]	0.0896	0.2856	0.006711	0.0	0.0	1.0	50001	5000
best2[7]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[8]	0.1068	0.3089	0.007261	0.0	0.0	1.0	50001	5000
best2[9]	0.1178	0.3224	0.007583	0.0	0.0	1.0	50001	5000
best2[10]	0.0202	0.1407	0.0025	0.0	0.0	0.0	50001	5000
best2[11]	0.0754	0.264	0.007277	0.0	0.0	1.0	50001	5000
best2[12]	0.1272	0.3332	0.007916	0.0	0.0	1.0	50001	5000
best2[13]	0.0546	0.2272	0.006064	0.0	0.0	1.0	50001	5000
best2[14]	0.0012	0.03462	6.173E-4	0.0	0.0	0.0	50001	5000
d[2]	0.8963	0.2501	0.009435	0.4273	0.89	1.407	50001	5000
d[3]	0.6082	0.4409	0.0188	-0.2297	0.6022	1.511	50001	5000
d[4]	1.027	0.3391	0.01314	0.3538	1.028	1.68	50001	5000
d[5]	0.1538	0.3677	0.01435	-0.6101	0.1626	0.8581	50001	5000
d[6]	0.9581	1.389	0.06647	-1.836	0.9836	3.633	50001	5000
d[7]	-1.279	0.5862	0.03166	-2.576	-1.248	-0.2382	50001	5000
d[8]	0.835	0.2937	0.01077	0.2566	0.8366	1.412	50001	5000
d[9]	0.7311	0.5374	0.02237	-0.4009	0.7564	1.73	50001	5000
d[10]	0.3228	0.4516	0.01741	-0.6187	0.3393	1.142	50001	5000
d[11]	0.3754	0.7572	0.03379	-1.117	0.3614	1.872	50001	5000
d[12]	0.8049	0.774	0.0374	-0.7337	0.7941	2.314	50001	5000
d[13]	0.6026	0.3885	0.01581	-0.1822	0.6048	1.338	50001	5000
d[14]	-0.1252	0.4832	0.01961	-1.104	-0.1081	0.8008	50001	5000
or[1,2]	0.4209	0.1051	0.003949	0.2449	0.4107	0.6522	50001	5000
or[1,3]	0.5994	0.2768	0.01133	0.2221	0.5476	1.259	50001	5000
or[1,4]	0.3793	0.134	0.005079	0.1865	0.3577	0.7047	50001	5000

or[1,5]	0.9189	0.3654	0.01358	0.4247	0.8499	1.842	50001	5000
or[1,6]	1.084	3.244	0.09586	0.02646	0.374	6.29	50001	5000
or[1,7]	4.363	3.563	0.1932	1.271	3.485	13.19	50001	5000
or[1,8]	0.453	0.136	0.004874	0.2438	0.4334	0.7739	50001	5000
or[1,9]	0.5604	0.3592	0.01455	0.1777	0.4695	1.493	50001	5000
or[1,10]	0.8048	0.4076	0.01548	0.3192	0.7124	1.859	50001	5000
or[1,11]	0.9148	0.8	0.03459	0.1547	0.6974	3.076	50001	5000
or[1,12]	0.6052	0.5691	0.02506	0.09896	0.4524	2.094	50001	5000
or[1,13]	0.5906	0.2411	0.00919	0.2624	0.5463	1.2	50001	5000
or[1,14]	1.28	0.7213	0.02903	0.4519	1.114	3.018	50001	5000
or[2,1]	2.53	0.6745	0.02498	1.533	2.435	4.085	50001	5000
or[2,2]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[2,3]	1.51	0.7924	0.03196	0.4867	1.342	3.517	50001	5000
or[2,4]	0.9466	0.3925	0.01426	0.414	0.8789	1.923	50001	5000
or[2,5]	2.31	1.1	0.04071	0.9095	2.085	4.987	50001	5000
or[2,6]	2.707	7.211	0.226	0.06141	0.9095	16.66	50001	5000
or[2,7]	11.02	9.848	0.4998	2.897	8.453	34.61	50001	5000
or[2,8]	1.13	0.422	0.01554	0.5463	1.054	2.162	50001	5000
or[2,9]	1.423	1.063	0.04281	0.3974	1.158	4.178	50001	5000
or[2,10]	2.036	1.211	0.04509	0.6819	1.746	5.162	50001	5000
or[2,11]	2.333	2.279	0.09269	0.3442	1.704	8.29	50001	5000
or[2,12]	1.532	1.555	0.06726	0.2188	1.105	5.5	50001	5000
or[2,13]	1.488	0.7274	0.03013	0.5534	1.35	3.315	50001	5000
or[2,14]	3.228	2.05	0.07553	0.9813	2.722	8.458	50001	5000
or[3,1]	2.029	0.9873	0.04067	0.7948	1.826	4.53	50001	5000
or[3,2]	0.8534	0.4911	0.02012	0.2849	0.7452	2.055	50001	5000
or[3,3]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[3,4]	0.7713	0.4993	0.01918	0.23	0.6577	2.072	50001	5000
or[3,5]	1.822	1.115	0.04282	0.5741	1.552	4.89	50001	5000
or[3,6]	2.101	6.734	0.1831	0.04494	0.6867	12.55	50001	5000
or[3,7]	8.794	9.033	0.4293	1.779	6.295	30.62	50001	5000
or[3,8]	0.9127	0.5196	0.0201	0.2967	0.787	2.253	50001	5000
or[3,9]	1.124	0.932	0.03152	0.2441	0.8571	3.513	50001	5000
or[3,10]	1.625	1.191	0.04517	0.4179	1.31	4.691	50001	5000
or[3,11]	1.871	2.119	0.08808	0.2115	1.262	7.458	50001	5000
or[3,12]	1.21	1.407	0.05683	0.1496	0.8272	4.563	50001	5000
or[3,13]	1.165	0.7054	0.02566	0.3549	0.9926	2.982	50001	5000
or[3,14]	2.542	1.936	0.06991	0.6406	2.041	7.402	50001	5000
or[4,1]	2.959	1.048	0.03958	1.424	2.796	5.368	50001	5000
or[4,2]	1.228	0.4945	0.01842	0.5208	1.138	2.417	50001	5000
or[4,3]	1.773	1.08	0.04335	0.485	1.521	4.362	50001	5000
or[4,4]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[4,5]	2.701	1.453	0.0521	0.9572	2.37	6.358	50001	5000
or[4,6]	3.143	10.12	0.2869	0.0697	1.057	17.98	50001	5000
or[4,7]	12.89	12.09	0.6136	2.881	9.684	43.23	50001	5000
or[4,8]	1.33	0.5986	0.02199	0.5087	1.219	2.773	50001	5000
or[4,9]	1.648	1.235	0.04849	0.3987	1.339	4.824	50001	5000
or[4,10]	2.379	1.528	0.05204	0.7001	2.005	6.377	50001	5000
or[4,11]	2.688	2.664	0.1115	0.3824	1.911	9.943	50001	5000
or[4,12]	1.812	2.094	0.09474	0.2362	1.285	6.719	50001	5000
or[4,13]	1.742	0.9673	0.03607	0.565	1.535	4.161	50001	5000
or[4,14]	3.763	2.503	0.09802	1.048	3.126	10.24	50001	5000
or[5,1]	1.246	0.4618	0.0177	0.5433	1.177	2.359	50001	5000
or[5,2]	0.5213	0.2299	0.008892	0.2009	0.4797	1.105	50001	5000
or[5,3]	0.7281	0.4019	0.01537	0.2047	0.6445	1.742	50001	5000
or[5,4]	0.4689	0.2387	0.00845	0.1574	0.4219	1.046	50001	5000
or[5,5]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[5,6]	1.329	4.924	0.1203	0.02814	0.4363	8.032	50001	5000
or[5,7]	5.09	4.004	0.2086	1.452	4.053	14.57	50001	5000
or[5,8]	0.5502	0.2302	0.007781	0.2138	0.5144	1.115	50001	5000
or[5,9]	0.6607	0.4615	0.01614	0.1991	0.5547	1.72	50001	5000
or[5,10]	0.9541	0.5144	0.01831	0.3298	0.8341	2.3	50001	5000

or[5,11]	1.142	1.22	0.05539	0.1486	0.8099	4.217	50001	5000
or[5,12]	0.736	0.7612	0.03315	0.09378	0.5302	2.577	50001	5000
or[5,13]	0.7199	0.3685	0.01425	0.2314	0.6431	1.664	50001	5000
or[5,14]	1.453	0.718	0.0272	0.5855	1.303	3.194	50001	5000
or[6,1]	6.687	14.58	0.5624	0.1595	2.674	37.81	50001	5000
or[6,2]	2.825	6.383	0.2363	0.06025	1.1	16.3	50001	5000
or[6,3]	3.872	8.558	0.3288	0.07971	1.458	22.76	50001	5000
or[6,4]	2.558	6.361	0.233	0.05573	0.9466	14.42	50001	5000
or[6,5]	5.961	13.61	0.4665	0.125	2.296	36.1	50001	5000
or[6,6]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[6,7]	27.46	75.76	1.991	0.4817	9.548	159.9	50001	5000
or[6,8]	3.039	6.884	0.2493	0.06875	1.162	18.2	50001	5000
or[6,9]	3.781	9.956	0.3078	0.06009	1.241	24.97	50001	5000
or[6,10]	5.148	12.65	0.3837	0.1034	1.96	29.1	50001	5000
or[6,11]	5.679	15.12	0.5558	0.07721	1.88	33.31	50001	5000
or[6,12]	3.737	9.803	0.3142	0.04831	1.182	23.58	50001	5000
or[6,13]	3.985	9.449	0.3627	0.07632	1.479	24.63	50001	5000
or[6,14]	8.049	18.16	0.6391	0.1501	3.041	47.71	50001	5000
or[7,1]	0.3258	0.1848	0.008788	0.07605	0.2871	0.788	50001	5000
or[7,2]	0.1364	0.08471	0.003891	0.02902	0.1183	0.3469	50001	5000
or[7,3]	0.193	0.1465	0.006358	0.03282	0.1589	0.5631	50001	5000
or[7,4]	0.1232	0.08512	0.003776	0.02317	0.1033	0.3472	50001	5000
or[7,5]	0.2819	0.1701	0.007441	0.06881	0.2468	0.6891	50001	5000
or[7,6]	0.3295	0.917	0.02434	0.006258	0.1049	2.086	50001	5000
or[7,7]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[7,8]	0.1447	0.09074	0.004176	0.03113	0.1258	0.366	50001	5000
or[7,9]	0.1757	0.1553	0.005676	0.02997	0.1334	0.576	50001	5000
or[7,10]	0.254	0.1983	0.007711	0.04845	0.2028	0.7786	50001	5000
or[7,11]	0.3001	0.3727	0.01662	0.0277	0.1919	1.247	50001	5000
or[7,12]	0.1791	0.1829	0.007472	0.02183	0.1285	0.6609	50001	5000
or[7,13]	0.1914	0.1367	0.005824	0.03242	0.1604	0.5276	50001	5000
or[7,14]	0.3864	0.2802	0.01095	0.08454	0.3188	1.061	50001	5000
or[8,1]	2.407	0.7311	0.02678	1.293	2.308	4.103	50001	5000
or[8,2]	0.9971	0.348	0.01264	0.464	0.9488	1.834	50001	5000
or[8,3]	1.432	0.7873	0.02904	0.444	1.271	3.372	50001	5000
or[8,4]	0.9084	0.4339	0.01697	0.3611	0.8206	1.968	50001	5000
or[8,5]	2.158	0.9743	0.03447	0.8973	1.945	4.684	50001	5000
or[8,6]	2.576	9.39	0.2404	0.05526	0.8615	14.55	50001	5000
or[8,7]	10.3	9.012	0.4909	2.741	7.952	32.24	50001	5000
or[8,8]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[8,9]	1.342	0.967	0.03611	0.3583	1.1	3.829	50001	5000
or[8,10]	1.889	1.073	0.0413	0.6721	1.634	4.593	50001	5000
or[8,11]	2.194	2.142	0.08761	0.3251	1.602	7.909	50001	5000
or[8,12]	1.448	1.494	0.06267	0.2047	1.031	5.177	50001	5000
or[8,13]	1.412	0.7162	0.02844	0.5042	1.263	3.19	50001	5000
or[8,14]	3.023	1.962	0.07545	0.9764	2.558	7.846	50001	5000
or[9,1]	2.389	1.337	0.05126	0.6697	2.131	5.638	50001	5000
or[9,2]	1.005	0.6335	0.02332	0.2398	0.8635	2.52	50001	5000
or[9,3]	1.419	1.117	0.04034	0.2855	1.167	4.097	50001	5000
or[9,4]	0.9031	0.6194	0.02453	0.2074	0.7467	2.509	50001	5000
or[9,5]	2.066	1.203	0.04032	0.583	1.803	5.03	50001	5000
or[9,6]	2.583	10.63	0.2691	0.04035	0.8058	16.64	50001	5000
or[9,7]	9.884	9.62	0.4089	1.748	7.496	33.38	50001	5000
or[9,8]	1.079	0.7072	0.02503	0.2613	0.9092	2.795	50001	5000
or[9,9]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[9,10]	1.886	1.465	0.04698	0.3927	1.51	5.813	50001	5000
or[9,11]	2.17	2.512	0.1081	0.2257	1.458	8.505	50001	5000
or[9,12]	1.385	1.495	0.05898	0.1437	0.9514	5.051	50001	5000
or[9,13]	1.376	0.8986	0.03282	0.3154	1.184	3.818	50001	5000
or[9,14]	2.84	1.933	0.06731	0.6867	2.349	7.86	50001	5000
or[10,1]	1.524	0.6921	0.02479	0.5387	1.404	3.135	50001	5000
or[10,2]	0.6398	0.3306	0.01231	0.1946	0.5727	1.468	50001	5000

or[10,3]	0.908	0.5991	0.02261	0.2135	0.7637	2.402	50001	5000
or[10,4]	0.5781	0.3509	0.01119	0.1583	0.4992	1.432	50001	5000
or[10,5]	1.334	0.7006	0.02231	0.4359	1.199	3.037	50001	5000
or[10,6]	1.651	5.83	0.1717	0.03448	0.5107	9.68	50001	5000
or[10,7]	6.392	6.034	0.2966	1.285	4.932	20.74	50001	5000
or[10,8]	0.6712	0.3283	0.01224	0.2182	0.6122	1.488	50001	5000
or[10,9]	0.839	0.7273	0.02277	0.1725	0.6622	2.551	50001	5000
or[10,10]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[10,11]	1.399	1.534	0.0626	0.169	0.9511	5.604	50001	5000
or[10,12]	0.9059	0.9913	0.03709	0.1022	0.6357	3.323	50001	5000
or[10,13]	0.8891	0.5405	0.01875	0.2292	0.7699	2.227	50001	5000
or[10,14]	1.875	1.31	0.03939	0.4782	1.582	5.116	50001	5000
or[11,1]	1.94	1.742	0.06864	0.3272	1.435	6.501	50001	5000
or[11,2]	0.8255	0.8313	0.03436	0.1209	0.5869	2.922	50001	5000
or[11,3]	1.171	1.324	0.05152	0.1353	0.7928	4.744	50001	5000
or[11,4]	0.7306	0.7523	0.02825	0.1006	0.5235	2.619	50001	5000
or[11,5]	1.779	1.852	0.07447	0.2375	1.235	6.738	50001	5000
or[11,6]	2.202	12.7	0.3005	0.0302	0.5321	13.01	50001	5000
or[11,7]	8.319	10.72	0.4271	0.8039	5.213	36.16	50001	5000
or[11,8]	0.8745	0.8281	0.03216	0.1265	0.6249	3.087	50001	5000
or[11,9]	1.096	1.468	0.05678	0.1177	0.6859	4.433	50001	5000
or[11,10]	1.554	1.695	0.06203	0.1787	1.052	5.918	50001	5000
or[11,11]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[11,12]	1.099	1.426	0.05324	0.08756	0.6519	4.922	50001	5000
or[11,13]	1.164	1.396	0.05161	0.1438	0.7964	4.275	50001	5000
or[11,14]	2.464	2.823	0.1087	0.2957	1.641	9.584	50001	5000
or[12,1]	3.019	2.728	0.122	0.4801	2.212	10.12	50001	5000
or[12,2]	1.272	1.247	0.05361	0.182	0.9053	4.576	50001	5000
or[12,3]	1.771	1.842	0.07722	0.2205	1.209	6.703	50001	5000
or[12,4]	1.148	1.187	0.05144	0.1496	0.7785	4.246	50001	5000
or[12,5]	2.732	2.809	0.1241	0.3908	1.887	10.69	50001	5000
or[12,6]	3.247	12.43	0.3681	0.04243	0.8466	20.73	50001	5000
or[12,7]	12.06	20.13	0.8092	1.517	7.784	46.0	50001	5000
or[12,8]	1.365	1.367	0.05698	0.1942	0.9702	4.889	50001	5000
or[12,9]	1.664	2.343	0.08221	0.1985	1.051	7.055	50001	5000
or[12,10]	2.402	2.635	0.1056	0.3011	1.575	9.789	50001	5000
or[12,11]	2.605	3.606	0.1499	0.205	1.535	11.44	50001	5000
or[12,12]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[12,13]	1.788	1.989	0.08766	0.2447	1.196	6.787	50001	5000
or[12,14]	3.767	5.174	0.1768	0.4726	2.493	14.93	50001	5000
or[13,1]	1.969	0.7901	0.03229	0.8334	1.831	3.811	50001	5000
or[13,2]	0.827	0.4029	0.01727	0.3024	0.741	1.812	50001	5000
or[13,3]	1.146	0.6514	0.02321	0.3371	1.008	2.82	50001	5000
or[13,4]	0.7436	0.3973	0.01534	0.243	0.6513	1.771	50001	5000
or[13,5]	1.776	0.9796	0.03893	0.6011	1.555	4.323	50001	5000
or[13,6]	2.227	8.874	0.2376	0.04068	0.6789	13.16	50001	5000
or[13,7]	8.643	8.352	0.4695	1.896	6.236	30.91	50001	5000
or[13,8]	0.8868	0.4481	0.01865	0.3142	0.7922	1.986	50001	5000
or[13,9]	1.08	0.7962	0.0327	0.262	0.8449	3.176	50001	5000
or[13,10]	1.571	1.043	0.03929	0.4518	1.299	4.367	50001	5000
or[13,11]	1.831	1.998	0.08443	0.2344	1.256	6.957	50001	5000
or[13,12]	1.168	1.202	0.04993	0.1475	0.8366	4.09	50001	5000
or[13,13]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[13,14]	2.433	1.612	0.06847	0.719	2.038	6.54	50001	5000
or[14,1]	0.9897	0.5043	0.01855	0.3315	0.8975	2.227	50001	5000
or[14,2]	0.4149	0.2382	0.008061	0.1186	0.3675	1.021	50001	5000
or[14,3]	0.5776	0.3821	0.01402	0.1355	0.4899	1.565	50001	5000
or[14,4]	0.3748	0.272	0.008874	0.09782	0.3199	0.9563	50001	5000
or[14,5]	0.8267	0.3658	0.01397	0.3137	0.768	1.712	50001	5000
or[14,6]	1.029	2.929	0.08762	0.021	0.3293	6.694	50001	5000
or[14,7]	3.921	3.07	0.1389	0.945	3.138	11.86	50001	5000
or[14,8]	0.4377	0.2405	0.008284	0.1282	0.391	1.025	50001	5000

or[14,9]	0.5165	0.3895	0.01389	0.1272	0.4258	1.467	50001	5000
or[14,10]	0.768	0.5631	0.01839	0.1955	0.6322	2.094	50001	5000
or[14,11]	0.9033	1.052	0.04219	0.1048	0.6098	3.382	50001	5000
or[14,12]	0.5724	0.609	0.02446	0.06724	0.4011	2.117	50001	5000
or[14,13]	0.5625	0.3377	0.01329	0.153	0.4908	1.393	50001	5000
or[14,14]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000

```
# Model - heterogeneous random effects model
# Assume correlation within study (rho = 0.5)
# Assume heterogeneous between studies ; "sdmu" is (0.01, 5)

model {
  for (i in 1:NS) {
    s[i,1] <- 0
    delta[i, t[i,1]] <- 0
    mu[i] ~ dnorm(mmu[t[i,1]], taumu)  # handle different baseline treatments

    for (k in 1:na[i]) {
      r[i,k] ~ dbin(p[i,t[i,k]], n[i,k])
      logit(p[i,t[i,k]]) <- mu[i] + delta[i,t[i,k]]
    }

    for (k in 2:na[i]) {
      delta[i,t[i,k]] ~ dnorm(md[i,t[i,k]], taud[i,t[i,k]])
      md[i,t[i,k]] <- d[t[i,k]] - d[t[i,1]] + ss[i,k]
      taud[i,t[i,k]] <- tau[t[i,1],t[i,k]]*2*(k-1)/k
      s[i,k] <- (delta[i, t[i,k]] - d[t[i,k]] + d[t[i,1]])
      ss[i,k] <- sum(s[i, 1:k-1])/(k-1)
    }
  }

  mmu[5] <- 0    #Treatments 1,2,3,4,6,7 are one of baseline treatments.
  mmu[8] <- 0    # other treatments should be assigned to 0.
  mmu[9] <- 0
  mmu[10] <- 0
  mmu[11] <- 0
mmu[12] <- 0
mmu[13] <- 0
mmu[14] <- 0
  mmu[1] ~ dnorm(0, 0.0001)
  mmu[2] ~ dnorm(0, 0.0001)
  mmu[3] ~ dnorm(0, 0.0001)
  mmu[4] ~ dnorm(0, 0.0001)
  mmu[6] ~ dnorm(0, 0.0001)
  mmu[7] ~ dnorm(0, 0.0001)
  sdmu ~ dunif(0.01, 5)
  taumu <- 1/pow(sdmu,2)

  d[1] <- 0
  for (k in 2:NT) {
    d[k] ~ dnorm(0,0.0001)
    ed[k] <- exp(d[k])         # ed is odds ratio against placebo
  }

  for(i in 1:(NT-1)) {
    for(j in (i+1):NT) {
      v[i,j] ~ dnorm(0, 8.32)
      log(sd[i,j]) <- log(sd0) + v[i,j]
      tau[i,j] <- 1/pow(sd[i,j],2)
      var[i,j] <- pow(sd[i,j],2)
    }
```

```
  }
  sd0 ~ dunif(0.01, 2)
  var0 <- pow(sd0,2)

  # pairwise ORs
  # Example: or[2,3] = odds ratio of active(2) vs. control(3)
  for (k in 1:NT) {
    for (c in 1:NT) {
      lor[k,c] <- d[k] - d[c]
      log(or[k,c]) <- lor[k,c]
    }
  }

  # ranking
  mP <- mmu[1]  # "mP" means the odds of placebo.

  for (k in 1:NT) { logit(T[k]) <- mP + d[k] }
  for (k in 1:NT) {
    rk[k] <- NT + 1 - rank(T[],k)
    best1[k] <- equals(rk[k],1)
    best2[k] <- equals(rk[k],2)
    best12[k] <- best1[k] + best2[k]
  }
}

#Init
list(
d=c(NA,0,0,0,0, 0,0,0,0,0,    0,0,0,0),
sd0=1,
mu=c(0,0,0,0,0,  0,0,0,0,0, 0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,
0,0,0,0,0,  0,0,0,0,0,  0,0,0,0,0,  0,0,0,0),
mmu=c(0,0,0,0,NA, 0,0,NA,NA,NA, NA,NA,NA,NA), sdmu=1
)


#Data


#Data
list(NT=14, NS=68)
```

r[,1]	n[,1]	r[,2]	n[,2]	r[,3]	n[,3]	t[,1]	t[,2]	t[,3]	na[]
1	96	2	96	NA	1	1	12	NA	2
2	61	5	55	NA	1	1	8	NA	2
1	83	6	83	NA	1	1	5	NA	2
3	48	5	46	NA	1	5	14	NA	2
2	32	1	32	NA	1	1	3	NA	2
1	75	10	74	NA	1	7	14	NA	2
5	20	13	20	NA	1	5	9	NA	2
5	24	9	31	NA	1	1	5	NA	2
4	46	3	43	NA	1	1	9	NA	2
4	44	2	47	NA	1	5	7	NA	2
2	34	4	31	NA	1	1	8	NA	2
0	31	4	31	NA	1	7	12	NA	2
0	48	1	48	NA	1	1	4	NA	2
2	74	1	74	NA	1	1	10	NA	2

0	47	2	47	NA	1	1	6	NA	2
1	37	1	34	NA	1	1	7	NA	2
2	37	9	70	NA	1	1	3	NA	2
2	43	4	43	NA	1	1	3	NA	2
0	38	3	43	NA	1	1	13	NA	2
1	34	3	35	NA	1	1	13	NA	2
3	40	7	18	NA	1	1	4	NA	2
2	38	7	77	NA	1	1	7	NA	2
4	37	1	37	NA	1	3	5	NA	2
4	26	4	27	NA	1	1	8	NA	2
4	45	16	98	NA	1	1	4	NA	2
6	69	1	66	NA	1	13	14	NA	2
5	20	4	20	NA	1	5	10	NA	2
2	27	9	26	NA	1	1	4	NA	2
18	270	19	275	NA	1	5	14	NA	2
10	116	10	123	NA	1	1	3	NA	2
4	64	9	72	NA	1	1	13	NA	2
0	36	6	34	NA	1	1	2	NA	2
2	84	2	93	NA	1	1	13	NA	2
2	57	3	58	NA	1	1	2	NA	2
6	20	9	30	NA	1	1	2	NA	2
4	73	21	140	NA	1	1	2	NA	2
10	163	18	165	NA	1	1	2	NA	2
3	60	3	60	3	60	1	2	4	3
41	383	96	391	NA	1	1	2	NA	2
10	45	0	45	NA	1	2	13	NA	2
4	85	8	85	NA	1	1	4	NA	2
3	58	2	67	NA	1	3	13	NA	2
2	24	4	28	NA	1	2	8	NA	2
1	65	2	59	NA	1	1	13	NA	2
35	178	38	169	NA	1	2	8	NA	2
18	197	21	188	NA	1	1	2	NA	2
13	197	23	194	NA	1	1	8	NA	2
0	28	3	28	NA	1	1	7	NA	2
0	71	2	71	NA	1	1	12	NA	2
1	38	2	38	NA	1	1	11	NA	2
1	33	0	33	NA	1	1	9	NA	2
0	40	1	40	NA	1	1	11	NA	2
3	72	0	72	NA	1	1	7	NA	2
3	45	0	45	NA	1	1	10	NA	2
1	24	5	24	NA	1	1	9	NA	2

5	75	12	75	NA	1	1	10	NA	2
4	54	0	48	NA	1	13	14	NA	2
3	21	2	20	NA	1	8	10	NA	2
0	29	3	29	NA	1	5	8	NA	2
2	30	3	29	NA	1	1	8	NA	2
1	14	2	18	NA	1	9	14	NA	2
1	22	2	23	NA	1	1	4	NA	2
1	46	2	46	NA	1	1	11	NA	2
3	32	2	27	NA	1	5	14	NA	2
2	20	13	62	NA	1	1	4	NA	2
1	13	0	15	NA	1	2	4	NA	2
0	63	18	63	NA	1	7	8	NA	2
3	48	3	44	9	49	5	8	10	3

END

node	mean	sd	MC error	2.5%	median	97.5%	start	sample
best1[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[2]	0.048	0.2138	0.005892	0.0	0.0	1.0	50001	5000
best1[3]	0.0462	0.2099	0.005419	0.0	0.0	1.0	50001	5000
best1[4]	0.1536	0.3606	0.01422	0.0	0.0	1.0	50001	5000
best1[5]	2.0E-4	0.01414	2.006E-4	0.0	0.0	0.0	50001	5000
best1[6]	0.3488	0.4766	0.02233	0.0	0.0	1.0	50001	5000
best1[7]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best1[8]	0.0428	0.2024	0.005105	0.0	0.0	1.0	50001	5000
best1[9]	0.0978	0.297	0.009791	0.0	0.0	1.0	50001	5000
best1[10]	0.0078	0.08797	0.001628	0.0	0.0	0.0	50001	5000
best1[11]	0.0828	0.2756	0.008454	0.0	0.0	1.0	50001	5000
best1[12]	0.1458	0.3529	0.01337	0.0	0.0	1.0	50001	5000
best1[13]	0.0252	0.1567	0.003928	0.0	0.0	1.0	50001	5000
best1[14]	0.001	0.03161	4.331E-4	0.0	0.0	0.0	50001	5000
best2[1]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[2]	0.1408	0.3478	0.008127	0.0	0.0	1.0	50001	5000
best2[3]	0.075	0.2634	0.006685	0.0	0.0	1.0	50001	5000
best2[4]	0.203	0.4022	0.008737	0.0	0.0	1.0	50001	5000
best2[5]	0.0038	0.06153	0.001243	0.0	0.0	0.0	50001	5000
best2[6]	0.0808	0.2725	0.006052	0.0	0.0	1.0	50001	5000
best2[7]	0.0	0.0	1.414E-12	0.0	0.0	0.0	50001	5000
best2[8]	0.108	0.3104	0.007817	0.0	0.0	1.0	50001	5000
best2[9]	0.1238	0.3294	0.007522	0.0	0.0	1.0	50001	5000
best2[10]	0.0182	0.1337	0.002555	0.0	0.0	0.0	50001	5000
best2[11]	0.084	0.2774	0.007281	0.0	0.0	1.0	50001	5000
best2[12]	0.1032	0.3042	0.006101	0.0	0.0	1.0	50001	5000
best2[13]	0.0586	0.2349	0.005443	0.0	0.0	1.0	50001	5000
best2[14]	8.0E-4	0.02827	3.884E-4	0.0	0.0	0.0	50001	5000
d[2]	0.8884	0.2447	0.008527	0.4178	0.8806	1.405	50001	5000
d[3]	0.6419	0.4462	0.0205	-0.1735	0.6181	1.559	50001	5000
d[4]	1.007	0.3599	0.01703	0.3205	1.005	1.705	50001	5000
d[5]	0.1856	0.3805	0.01226	-0.5701	0.1883	0.9327	50001	5000
d[6]	0.8932	1.431	0.06919	-1.87	0.9052	3.751	50001	5000
d[7]	-1.255	0.6031	0.03536	-2.619	-1.213	-0.1867	50001	5000
d[8]	0.8291	0.297	0.01152	0.2442	0.8268	1.423	50001	5000
d[9]	0.7334	0.5474	0.02262	-0.3835	0.7485	1.79	50001	5000
d[10]	0.3362	0.4494	0.01653	-0.5891	0.3491	1.185	50001	5000
d[11]	0.4371	0.7837	0.03416	-1.104	0.4526	1.968	50001	5000
d[12]	0.6907	0.7517	0.03829	-0.7297	0.6485	2.29	50001	5000
d[13]	0.628	0.408	0.01746	-0.1904	0.6351	1.439	50001	5000

d[14]	-0.1063	0.4735	0.01603	-1.091	-0.08985	0.7978	50001	5000
or[1,2]	0.4237	0.1035	0.003432	0.2458	0.4146	0.6585	50001	5000
or[1,3]	0.5796	0.2609	0.01139	0.2108	0.5391	1.19	50001	5000
or[1,4]	0.3904	0.1586	0.006856	0.1827	0.3661	0.7261	50001	5000
or[1,5]	0.8941	0.3665	0.01132	0.3939	0.8284	1.769	50001	5000
or[1,6]	1.162	3.709	0.08424	0.02351	0.4052	6.59	50001	5000
or[1,7]	4.286	3.394	0.1849	1.206	3.367	13.75	50001	5000
or[1,8]	0.4561	0.1398	0.005236	0.2411	0.4375	0.7836	50001	5000
or[1,9]	0.5608	0.356	0.01477	0.1671	0.4732	1.471	50001	5000
or[1,10]	0.7924	0.3933	0.01398	0.3062	0.7055	1.802	50001	5000
or[1,11]	0.912	1.343	0.05316	0.1404	0.6364	3.074	50001	5000
or[1,12]	0.6551	0.5299	0.02391	0.1014	0.5228	2.081	50001	5000
or[1,13]	0.5803	0.251	0.01071	0.2379	0.5299	1.211	50001	5000
or[1,14]	1.248	0.6642	0.02216	0.4505	1.095	2.978	50001	5000
or[2,1]	2.506	0.6435	0.02315	1.519	2.412	4.075	50001	5000
or[2,2]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[2,3]	1.454	0.7815	0.0324	0.4617	1.301	3.444	50001	5000
or[2,4]	0.9714	0.4664	0.01974	0.396	0.8869	2.027	50001	5000
or[2,5]	2.22	1.037	0.03343	0.8734	2.014	4.776	50001	5000
or[2,6]	2.924	8.867	0.2072	0.05464	0.9733	16.59	50001	5000
or[2,7]	10.63	8.71	0.4469	2.691	8.196	34.34	50001	5000
or[2,8]	1.126	0.4092	0.01374	0.5473	1.056	2.154	50001	5000
or[2,9]	1.403	0.996	0.03809	0.3775	1.141	4.104	50001	5000
or[2,10]	1.979	1.141	0.03941	0.6801	1.719	4.933	50001	5000
or[2,11]	2.322	3.883	0.1484	0.2986	1.55	8.424	50001	5000
or[2,12]	1.636	1.416	0.05834	0.2371	1.271	5.365	50001	5000
or[2,13]	1.435	0.6778	0.02578	0.5232	1.299	3.142	50001	5000
or[2,14]	3.107	1.816	0.06276	0.9814	2.662	7.901	50001	5000
or[3,1]	2.107	1.054	0.04751	0.8407	1.855	4.753	50001	5000
or[3,2]	0.8942	0.5264	0.02137	0.2916	0.7691	2.169	50001	5000
or[3,3]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[3,4]	0.817	0.5401	0.01969	0.2476	0.6791	2.186	50001	5000
or[3,5]	1.85	1.214	0.04808	0.553	1.561	4.954	50001	5000
or[3,6]	2.571	9.575	0.2364	0.04141	0.7706	15.43	50001	5000
or[3,7]	8.957	8.736	0.4769	1.691	6.465	33.01	50001	5000
or[3,8]	0.9575	0.5823	0.02467	0.2998	0.823	2.394	50001	5000
or[3,9]	1.193	1.108	0.05082	0.245	0.8856	3.944	50001	5000
or[3,10]	1.655	1.205	0.05222	0.422	1.333	4.984	50001	5000
or[3,11]	1.925	2.915	0.1106	0.2249	1.188	7.52	50001	5000
or[3,12]	1.346	1.333	0.05546	0.1723	0.9671	4.549	50001	5000
or[3,13]	1.184	0.7383	0.03288	0.3596	1.009	3.083	50001	5000
or[3,14]	2.591	1.989	0.07751	0.673	2.045	7.561	50001	5000
or[4,1]	2.92	1.081	0.05138	1.378	2.732	5.503	50001	5000
or[4,2]	1.228	0.5373	0.02447	0.4934	1.128	2.529	50001	5000
or[4,3]	1.674	0.9534	0.03791	0.4579	1.473	4.047	50001	5000
or[4,4]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[4,5]	2.597	1.466	0.05993	0.8501	2.25	6.507	50001	5000
or[4,6]	3.364	9.847	0.2425	0.0588	1.134	19.33	50001	5000
or[4,7]	12.52	11.76	0.5937	2.786	9.249	42.29	50001	5000
or[4,8]	1.33	0.6604	0.0291	0.503	1.177	3.03	50001	5000
or[4,9]	1.638	1.351	0.05941	0.3833	1.291	4.924	50001	5000
or[4,10]	2.311	1.511	0.0619	0.6503	1.912	6.247	50001	5000
or[4,11]	2.638	4.659	0.1637	0.339	1.755	9.104	50001	5000
or[4,12]	1.921	1.897	0.08342	0.2371	1.406	6.604	50001	5000
or[4,13]	1.683	0.9775	0.04343	0.5341	1.438	4.191	50001	5000
or[4,14]	3.618	2.412	0.08986	0.986	3.019	9.827	50001	5000
or[5,1]	1.293	0.5076	0.01625	0.5655	1.207	2.541	50001	5000
or[5,2]	0.5437	0.2488	0.008208	0.2096	0.4965	1.148	50001	5000
or[5,3]	0.7363	0.435	0.0186	0.2024	0.6408	1.811	50001	5000
or[5,4]	0.5009	0.2826	0.01052	0.1544	0.4446	1.177	50001	5000
or[5,5]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[5,6]	1.543	5.359	0.1199	0.02631	0.4881	9.104	50001	5000

or[5,7]	5.152	3.869	0.1929	1.374	4.09	15.81	50001	5000
or[5,8]	0.5709	0.244	0.00831	0.2345	0.5258	1.163	50001	5000
or[5,9]	0.6798	0.4572	0.01635	0.1995	0.5773	1.847	50001	5000
or[5,10]	0.9744	0.55	0.02149	0.3534	0.8456	2.304	50001	5000
or[5,11]	1.17	1.69	0.06378	0.1385	0.7688	4.46	50001	5000
or[5,12]	0.8274	0.7658	0.03029	0.109	0.6223	2.857	50001	5000
or[5,13]	0.7321	0.402	0.01582	0.2287	0.6449	1.767	50001	5000
or[5,14]	1.458	0.6572	0.0222	0.6313	1.315	3.176	50001	5000
or[6,1]	7.504	38.38	0.9885	0.1541	2.473	42.56	50001	5000
or[6,2]	3.182	15.66	0.4102	0.0603	1.028	18.31	50001	5000
or[6,3]	4.054	13.49	0.4374	0.06494	1.3	24.17	50001	5000
or[6,4]	3.074	18.56	0.4447	0.05255	0.8825	17.05	50001	5000
or[6,5]	6.506	22.45	0.7846	0.1111	2.049	38.19	50001	5000
or[6,6]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[6,7]	35.7	220.7	6.824	0.4368	8.754	205.9	50001	5000
or[6,8]	3.34	16.34	0.4179	0.06119	1.1	19.23	50001	5000
or[6,9]	4.584	28.8	0.8018	0.06188	1.144	24.2	50001	5000
or[6,10]	5.836	27.5	0.7544	0.09604	1.758	34.52	50001	5000
or[6,11]	7.185	58.91	1.288	0.06919	1.586	41.01	50001	5000
or[6,12]	4.867	18.32	0.5596	0.05313	1.19	30.0	50001	5000
or[6,13]	4.38	28.4	0.6474	0.0725	1.34	23.36	50001	5000
or[6,14]	8.697	29.33	0.9367	0.1499	2.758	51.76	50001	5000
or[7,1]	0.3372	0.1988	0.01084	0.07289	0.2972	0.8297	50001	5000
or[7,2]	0.1419	0.09073	0.004796	0.02916	0.1221	0.372	50001	5000
or[7,3]	0.1943	0.1519	0.008551	0.0304	0.1547	0.5939	50001	5000
or[7,4]	0.1303	0.09098	0.004251	0.02377	0.1081	0.3591	50001	5000
or[7,5]	0.2829	0.1787	0.008634	0.06351	0.2446	0.7281	50001	5000
or[7,6]	0.391	1.269	0.0295	0.004867	0.1143	2.294	50001	5000
or[7,7]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[7,8]	0.1497	0.09705	0.005185	0.03278	0.1283	0.3936	50001	5000
or[7,9]	0.1781	0.1458	0.006522	0.03062	0.1402	0.5419	50001	5000
or[7,10]	0.2589	0.2069	0.009831	0.04803	0.2047	0.7741	50001	5000
or[7,11]	0.2922	0.3652	0.01436	0.02506	0.1839	1.149	50001	5000
or[7,12]	0.2086	0.198	0.009478	0.01845	0.1514	0.7039	50001	5000
or[7,13]	0.1902	0.1384	0.006839	0.03512	0.1561	0.5519	50001	5000
or[7,14]	0.3862	0.2732	0.01226	0.08535	0.3224	1.097	50001	5000
or[8,1]	2.396	0.7441	0.02871	1.277	2.286	4.149	50001	5000
or[8,2]	0.9985	0.3517	0.01185	0.4662	0.9467	1.829	50001	5000
or[8,3]	1.383	0.7698	0.03313	0.4208	1.216	3.344	50001	5000
or[8,4]	0.9293	0.452	0.01896	0.3303	0.8496	1.989	50001	5000
or[8,5]	2.072	0.9183	0.0318	0.8601	1.903	4.264	50001	5000
or[8,6]	2.862	11.56	0.2297	0.05218	0.9094	16.35	50001	5000
or[8,7]	9.889	7.63	0.4251	2.546	7.798	30.6	50001	5000
or[8,8]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[8,9]	1.316	0.9113	0.03563	0.3493	1.085	3.722	50001	5000
or[8,10]	1.842	0.9964	0.03721	0.6556	1.62	4.357	50001	5000
or[8,11]	2.183	3.392	0.1356	0.2906	1.454	7.751	50001	5000
or[8,12]	1.546	1.324	0.0551	0.2174	1.191	5.178	50001	5000
or[8,13]	1.377	0.7219	0.02917	0.4723	1.22	3.327	50001	5000
or[8,14]	2.907	1.659	0.05733	0.9608	2.529	7.386	50001	5000
or[9,1]	2.41	1.383	0.05116	0.6814	2.114	5.992	50001	5000
or[9,2]	1.013	0.6203	0.0216	0.244	0.877	2.655	50001	5000
or[9,3]	1.4	1.127	0.04397	0.2552	1.13	4.085	50001	5000
or[9,4]	0.9295	0.655	0.02357	0.2034	0.7748	2.613	50001	5000
or[9,5]	2.016	1.217	0.04308	0.5418	1.733	5.032	50001	5000
or[9,6]	2.775	10.69	0.2339	0.04137	0.8762	16.42	50001	5000
or[9,7]	9.74	9.157	0.4377	1.851	7.135	32.9	50001	5000
or[9,8]	1.077	0.6784	0.02428	0.2698	0.9217	2.871	50001	5000
or[9,9]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[9,10]	1.844	1.402	0.05056	0.4228	1.497	5.535	50001	5000
or[9,11]	2.153	3.17	0.1244	0.2086	1.318	8.975	50001	5000
or[9,12]	1.545	1.607	0.06097	0.1568	1.083	5.726	50001	5000

or[9,13]	1.368	0.966	0.03683	0.2864	1.123	3.913	50001	5000
or[9,14]	2.773	1.866	0.06669	0.7011	2.323	7.591	50001	5000
or[10,1]	1.546	0.7207	0.02484	0.5549	1.418	3.271	50001	5000
or[10,2]	0.6505	0.3346	0.01126	0.2029	0.5818	1.475	50001	5000
or[10,3]	0.8877	0.5926	0.02422	0.2011	0.7503	2.381	50001	5000
or[10,4]	0.6001	0.3803	0.01313	0.161	0.523	1.538	50001	5000
or[10,5]	1.303	0.6333	0.02443	0.4376	1.183	2.83	50001	5000
or[10,6]	1.715	4.617	0.1106	0.02904	0.5706	10.54	50001	5000
or[10,7]	6.297	5.347	0.2482	1.293	4.885	20.84	50001	5000
or[10,8]	0.684	0.3436	0.0126	0.2298	0.6175	1.527	50001	5000
or[10,9]	0.8325	0.6297	0.024	0.1814	0.6683	2.39	50001	5000
or[10,10]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[10,11]	1.394	2.209	0.07881	0.1517	0.8892	5.307	50001	5000
or[10,12]	0.9935	0.94	0.04193	0.1137	0.7385	3.569	50001	5000
or[10,13]	0.8766	0.5291	0.01964	0.2223	0.7625	2.186	50001	5000
or[10,14]	1.837	1.182	0.04017	0.4724	1.563	4.747	50001	5000
or[11,1]	2.089	1.882	0.07924	0.3314	1.572	7.157	50001	5000
or[11,2]	0.8902	0.8863	0.03657	0.119	0.6453	3.352	50001	5000
or[11,3]	1.195	1.204	0.04714	0.133	0.842	4.462	50001	5000
or[11,4]	0.8042	0.8367	0.03145	0.1099	0.57	2.956	50001	5000
or[11,5]	1.864	1.943	0.07894	0.2244	1.301	7.254	50001	5000
or[11,6]	2.303	6.956	0.1805	0.02448	0.6307	14.52	50001	5000
or[11,7]	8.994	13.37	0.5397	0.871	5.444	39.92	50001	5000
or[11,8]	0.9484	0.9645	0.04113	0.129	0.6879	3.46	50001	5000
or[11,9]	1.161	1.394	0.05339	0.1117	0.7589	4.817	50001	5000
or[11,10]	1.647	1.882	0.07385	0.1888	1.125	6.638	50001	5000
or[11,11]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[11,12]	1.34	1.796	0.06115	0.07952	0.8094	6.135	50001	5000
or[11,13]	1.209	1.281	0.05074	0.1422	0.8254	4.524	50001	5000
or[11,14]	2.609	3.286	0.1205	0.2914	1.746	10.43	50001	5000
or[12,1]	2.713	2.801	0.1351	0.482	1.913	9.874	50001	5000
or[12,2]	1.15	1.316	0.0608	0.1871	0.7867	4.219	50001	5000
or[12,3]	1.526	1.743	0.08473	0.2206	1.034	5.814	50001	5000
or[12,4]	1.07	1.334	0.06243	0.1523	0.7112	4.23	50001	5000
or[12,5]	2.363	2.669	0.115	0.3501	1.609	9.172	50001	5000
or[12,6]	3.296	17.54	0.4395	0.0335	0.8405	18.89	50001	5000
or[12,7]	11.34	16.71	0.779	1.424	6.608	54.21	50001	5000
or[12,8]	1.225	1.386	0.05917	0.1932	0.8399	4.613	50001	5000
or[12,9]	1.529	2.363	0.09219	0.1758	0.9239	6.383	50001	5000
or[12,10]	2.125	2.574	0.1034	0.2815	1.354	8.815	50001	5000
or[12,11]	2.489	5.524	0.1886	0.1633	1.236	12.61	50001	5000
or[12,12]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[12,13]	1.568	1.89	0.09652	0.2179	1.04	6.292	50001	5000
or[12,14]	3.292	4.58	0.1919	0.4555	2.142	13.35	50001	5000
or[13,1]	2.037	0.8763	0.03607	0.8266	1.887	4.216	50001	5000
or[13,2]	0.8543	0.417	0.01586	0.3188	0.7698	1.92	50001	5000
or[13,3]	1.144	0.6579	0.0282	0.3245	0.9923	2.788	50001	5000
or[13,4]	0.7862	0.4515	0.01745	0.2389	0.6954	1.878	50001	5000
or[13,5]	1.781	1.033	0.03877	0.566	1.551	4.382	50001	5000
or[13,6]	2.323	6.847	0.1606	0.04297	0.7478	13.82	50001	5000
or[13,7]	8.419	7.119	0.3595	1.812	6.407	28.47	50001	5000
or[13,8]	0.9197	0.4795	0.01828	0.3015	0.8195	2.118	50001	5000
or[13,9]	1.124	0.9055	0.03878	0.2557	0.8902	3.494	50001	5000
or[13,10]	1.589	1.061	0.03495	0.4587	1.312	4.5	50001	5000
or[13,11]	1.849	3.026	0.1235	0.2216	1.214	7.113	50001	5000
or[13,12]	1.319	1.248	0.05894	0.1594	0.962	4.598	50001	5000
or[13,13]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000
or[13,14]	2.435	1.558	0.06049	0.7364	2.06	6.715	50001	5000
or[14,1]	1.004	0.4964	0.01563	0.3358	0.9141	2.221	50001	5000
or[14,2]	0.4223	0.2284	0.007802	0.127	0.3757	1.02	50001	5000
or[14,3]	0.569	0.3634	0.01498	0.1326	0.4891	1.487	50001	5000
or[14,4]	0.3876	0.2434	0.008838	0.1019	0.3312	1.015	50001	5000

or[14,5]	0.8089	0.3324	0.01133	0.3149	0.7606	1.589	50001	5000
or[14,6]	1.165	4.4	0.1012	0.01933	0.3631	6.706	50001	5000
or[14,7]	3.878	2.904	0.1498	0.9141	3.102	11.73	50001	5000
or[14,8]	0.4451	0.2371	0.007788	0.1358	0.3954	1.042	50001	5000
or[14,9]	0.5176	0.3545	0.0131	0.1322	0.4306	1.428	50001	5000
or[14,10]	0.7604	0.4965	0.01762	0.2127	0.6404	2.128	50001	5000
or[14,11]	0.8778	1.068	0.03709	0.09612	0.5728	3.446	50001	5000
or[14,12]	0.6302	0.5992	0.02359	0.07555	0.4671	2.198	50001	5000
or[14,13]	0.5553	0.322	0.01296	0.1495	0.4855	1.359	50001	5000
or[14,14]	1.0	0.0	1.414E-12	1.0	1.0	1.0	50001	5000

Appendix C. Excluded Studies

Not Eligible Exposure

1. Pharmacological prevention of migraine: to be considered case by case. Prescrire International 2006 Oct; 15(85):184-8; PMID: 17128528.
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Appendix D. Evidence Tables

Appendix Table D1. Pharmacological groups and agents examined in randomized controlled trials for migraine prevention in adults

Pharmacological Group of the Drug in Active Group	Name of Drug in Active Group	The Anatomical Therapeutic Chemical (ATC) Classification System
ACE Inhibitors	Captopril	C09AA01
ACE Inhibitors	Lisinopril	C09AA03
Angiotensin II receptor blockers	Candesartan	C09CA06
Angiotensin II receptor blockers	Telmisartan	C09CA07
Antiadrenergic	Clonidine	C02AC01
Antiadrenergic	Guanfacine	C02AC02
Antidepressant	Amitriptyline	N06AA09
Antidepressant	Clomipramine	N06AA04
Antidepressant	Escitalopram	N06AB10
Antidepressant	Femoxetine	N06AB05
Antidepressant	Fluoxetine	N06AB03
Antidepressant	Fluvoxamine	N06AB08
Antidepressant	Mianserin	N06AX03
Antidepressant	Nortriptyline	N06AA10
Antidepressant	Venlafaxine	N06AX16
Antiepileptic	Acetazolamide	S01EC01
Antiepileptic	Carbamazepin	N03AF01
Antiepileptic	Divalproex	N03AG01
Antiepileptic	Gabapentin	N03AX12
Antiepileptic	Lamotrigine	N03AX09
Antiepileptic	Levetiracetam	N03AX14
Antiepileptic	Oxcarbazepine	N03AF02
Antiepileptic	Topiramate	N03AX11
Antiepileptic	Valproate	N03AG01
Antiepileptic	Vigabatrin	N03AG04
Antiepileptic	Zonisamide	N03AX15
Beta-blocker	Acebutolol	C07AB04
Beta-blocker	Alprenolol	C07AA01
Beta-blocker	Atenolol	C07AB03
Beta-blocker	Bisoprolol	C07AB07
Beta-blocker	Metoprolol	C07AB02
Beta-blocker	Nadolol	C07AA12
Beta-blocker	Nebivolol	C07AB12
Beta-blocker	Pindolol	C07AA03
Beta-blocker	Practolol	C07AB01
Beta-blocker	Propranolol	C07AA05
Beta-blocker	Timolol	C07AA06
Cortical spreading depression inhibitor	Tonabersat	Not available
Dopaminergic agent	Dihydroergocryptine	N04BC03
Ergot alkaloid	Dihydroergotamine	N02CA01
Ergot alkaloid	Lisuride	N02CA07
Ergot alkaloid	Methysergide	N02CA04
Magnesium	Magnesium	A12CC
Muscle relaxant	Tizanidine	M03BX02
Antiinflammatory and Antirheumatic Products, Nonsteroids	Aspirin	N02BA01
Antiinflammatory and Antirheumatic Products, Nonsteroids	Fenoprofen	M01AE04
Antiinflammatory and Antirheumatic Products, Nonsteroids	Flurbiprofen	M01AE09
Antiinflammatory and Antirheumatic Products, Nonsteroids	Indobufen	B01AC10
Antiinflammatory and Antirheumatic Products, Nonsteroids	Indomethacin	M01AB01
Antiinflammatory and Antirheumatic Products, Nonsteroids	Induprofen	Not available

Appendix Table D1. Pharmacological groups and agents examined in randomized controlled trials for migraine prevention in adults (continued)

Pharmacological Group of the Drug in Active Group	Name of Drug in Active Group	The Anatomical Therapeutic Chemical (ATC) Classification System
Antiinflammatory and Antirheumatic Products, Nonsteroids	Ketoprofen	M01AE03
Antiinflammatory and Antirheumatic Products, Nonsteroids	Naproxen	M01AE02
Antiinflammatory and Antirheumatic Products, Nonsteroids	Rofecoxib	M01AH02
Antiinflammatory and Antirheumatic Products, Nonsteroids	Tolfenamic Acid	M01AG02
Selective Calcium Channel Blockers	Nicardipine	C08CA04
Selective Calcium Channel Blockers	Nifedipine	C08CA05
Selective Calcium Channel Blockers	Nimodipine	C08CA06
Selective Calcium Channel Blockers	Verapamil	C08DA01
Leukotriene Receptor Antagonists	Montelukast	R03DC03

Appendix Table D2. Funding, ethical approval, and disclosure of conflict of interest in randomized controlled clinical trials of drugs for migraine prevention in adults

	COI not Disclosed	Disclosure of no COI	Disclosed COI	Funded by Grant	Funded by Industry	Funding not Reported	Funding from non Industry, not for Profit Sources	IRB Approval and Consent not Reported	Clear Reporting of IRB Approval and Consent	Total
Topiramate*	15	4	8	0	14	12	1	4	23	27
Divalproex*	0	0	3	0	3	0	0	1	2	3
Propranolol*	39	1	5	3	12	27	3	31	14	45
Timolol*	2	0	0	0	0	2	0	1	1	2
Acetazolamide	1	0	0	0	1	0	0	0	1	1
Gabapentin	4	0	0	0	1	3	0	3	1	4
Lamotrigine	1	0	0	0	0	1	0	0	1	1
Oxcarbazepine	0	0	1	0	1	0	0	0	1	1
Valproate	4	0	0	0	1	3	0	0	4	4
Vigabatrin	1	0	0	0	1	0	0	0	1	1
Carbamazepine	1	0	0	0	1	0	0	1	0	1
Alprenolol	1	0	0	0	0	1	0	1	0	1
Atenolol	2	0	0	0	0	2	0	2	0	2
Bisoprolol	1	0	0	0	1	0	0	0	1	1
Metoprolol	7	1	1	0	2	7	0	3	6	9
Nadolol	2	0	0	0	0	2	0	2	0	2
Pindolol	2	0	0	0	0	2	0	2	0	2
Acebutolol	1	0	0	1	0	0	0	1	0	1
Amitriptyline	3	0	1	0	2	2	0	2	2	4
Femoxetine	6	0	0	0	2	4	0	4	2	6
Fluoxetine	6	0	0	0	2	4	0	3	3	6
Fluvoxamine	1	0	0	0	0	1	0	1	0	1
Venlafaxine	3	0	0	0	2	1	0	1	2	3
Mianserin	1	0	0	0	1	0	0	1	0	1
Captopril	1	0	0	0	0	1	0	1	0	1
Lisinopril	0	0	1	0	1	0	0	0	1	1
Candesartan	0	0	1	0	1	0	0	0	1	1
Telmisartan	0	0	1	0	1	0	0	0	1	1
Nifedipine	1	0	0	0	0	1	0	1	0	1
Nimodipine	6	0	0	1	0	5	0	5	1	6
Verapamil	2	0	0	0	2	0	0	2	0	2
Nicardipine	1	0	0	0	1	0	0	1	0	1
Clonidine	14	0	0	0	7	7	0	13	1	14
Guanfacine	1	0	0	0	0	1	0	1	0	1

Appendix Table D2. Funding, ethical approval, and disclosure of conflict of interest in randomized controlled clinical trials of drugs for migraine prevention in adults (continued)

	COI not Disclosed	Disclosure of no COI	Disclosed COI	Funded by Grant	Funded by Industry	Funding not Reported	Funding from non Industry, not for Profit Sources	IRB Approval and Consent not Reported	Clear Reporting of IRB Approval and Consent	Total
Dihydroergocryptine	3	0	0	0	0	3	0	2	1	3
Dihydroergotamine	3	1	0	0	1	3	0	3	1	4
Lisuride	3	0	0	0	0	3	0	3	0	3
Methysergide	2	0	0	0	0	2	0	2	0	2
Non -drug	2	2	0	1	0	1	2	1	3	4
Aspirin	4	0	1	2	0	3	0	5	0	5
Fenoprofen	1	0	0	0	0	1	0	1	0	1
Flurbiprofen	1	0	0	0	1	0	0	0	1	1
Indobufen	1	0	0	0	0	1	0	1	0	1
Indomethacin	1	0	0	0	1	0	0	1	0	1
Induprofen	1	0	0	0	0	1	0	1	0	1
Ketoprofen	1	0	0	0	1	0	0	1	0	1
Naproxen sodium	3	0	0	1	1	1	0	2	1	3
Rofecoxib	1	0	0	0	0	1	0	1	0	1
Tolfenamic Acid	1	0	0	0	1	0	0	1	0	1
Magnesium	3	0	0	0	1	2	0	1	2	3
Montelukast	0	0	1	0	1	0	0	0	1	1
Tizanidine	1	0	0	0	1	0	0	1	0	1
Tonabersat	1	0	0	0	1	0	0	1	0	1
Total**	187	9	24	10	77	127	6	132	88	220
%	85	4.09	10.91	4.55	35	57.73	2.73	60	40	100

* approved drugs; **- including flunarizine trials COI = conflict of interest; IRB = Institutional Review Board

Appendix Table D3. Definition of migraine in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drugs	International Headache Society	Ad hoc Committee	Other Definitions	Not Reported	Total
Topiramate*	27	0	0	0	27
Divalproex*	3	0	0	0	3
Propranolol*	13	17	7	8	45
Timolol*	0	2	0	0	2
Acetazolamide	1	0	0	0	1
Gabapentin	3	0	1	0	4
Lamotrigine	1	0	0	0	1
Oxcarbazepine	1	0	0	0	1
Valproate	3	1	0	0	4
Vigabatrin	1	0	0	0	1
Carbamazepine	0	0	0	1	1
Alprenolol	0	1	0	0	1
Atenolol	0	2	0	0	2
Bisoprolol	0	0	0	1	1
Metoprolol	4	2	2	1	9
Nadolol	0	1	0	1	2
Pindolol	0	2	0	0	2
Acebutolol	1	0	0	0	1
Amitriptyline	1	2	0	1	4
Femoxetine	0	2	0	4	6
Fluoxetine	3	1	0	2	6
Fluvoxamine	1	0	0	0	1
Venlafaxine	3	0	0	0	3
Mianserin	0	0	0	1	1
Captopril	0	1	0	0	1
Lisinopril	1	0	0	0	1
Candesartan	1	0	0	0	1
Telmisartan	1	0	0	0	1
Nifedipine	1	0	0	0	1
Nimodipine	1	4	0	1	6
Verapamil	0	1	0	1	2
Nicardipine	1	0	0	0	1
Clonidine	1	7	0	6	14
Guanfacine	0	0	0	1	1
Dihydroergocryptine	2	0	0	1	3
Dihydroergotamine	1	3	0	0	4
Lisuride	2	0	0	1	3
Methysergide	1	1	0	0	2
Non -drug	4	0	0	0	4
Aspirin	1	2	1	1	5
Fenoprofen	0	1	0	0	1
Flurbiprofen	1	0	0	0	1
Indobufen	0	1	0	0	1
Indomethacin	0	0	0	1	1
Induprofen	0	1	0	0	1
Ketoprofen	0	1	0	0	1
Naproxen sodium	0	2	0	1	3
Rofecoxib	1	0	0	0	1
Tolfenamic Acid	0	1	0	0	1
Magnesium	2	1	0	0	3
Montelukast	1	0	0	0	1
Tizanidine	1	0	0	0	1
Tonabersat	1	0	0	0	1
Total	91	60	11	34	196**

* approved drugs; ** 24 flunarizine RCTs are not shown

Appendix Table D4. Total sample, weeks of followup, and percentage of loss of followup in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drug	Total Sample	# RCTs	Mean [Standard Deviation]	# RCTs	Weeks of Followup Mean [Standard Deviation]	# RCTs	% Loss of Followup Mean [Standard Deviation]
Topiramate*	5788	27	214.4 [209.1]	27	18.6 [6.5]	12	6.8 [5.8]
Divalproex*	522	3	174.0 [66.0]	3	12.0 [0.0]	3	1.2 [1.5]
Propranolol*	4630	42	110.2 [176.2]	45	18.6 [11.1]	36	12.3 [11.7]
Timolol*	121	2	60.5 [65.8]	2	20.0 [5.7]	Not reported	Not reported
Acetazolamide	53	1	53	1	12	1	0
Gabapentin	779	4	194.8 [225.1]	4	17.5 [6.4]	3	2.0 [3.5]
Lamotrigine	77	1	77	1	12	1	0
Oxcarbazepine	170	1	170	1	15	1	3.5
Valproate	244	4	61.0 [43.0]	4	17.0 [7.6]	4	11.9 [16.3]
Vigabatrin	23	1	23	1	28	1	0
Carbamazepine	Not reported	Not reported		1	12.0 [0.0]	1	6.3
Alprenolol	33	1	33	1	13.0 [0.0]	Not reported	Not reported
Atenolol	96	2	48.0 [33.9]	2	27.0 [1.4]	Not reported	Not reported
Bisoprolol	226	1	226	1	12.0 [0.0]	Not reported	Not reported
Metoprolol	687	9	76.3 [76.7]	9	16.7 [5.5]	Not reported	Not reported
Nadolol	112	2	56.0 [33.9]	2	12.0 [0.0]	Not reported	Not reported
Pindolol	58	2	29.0 [1.4]	2	7.5 [4.9]	Not reported	Not reported
Acebutolol	43	1	43	1	28.0 [0.0]	Not reported	Not reported
Amitriptyline	753	4	188.3 [135.4]	4	10.0 [7.7]	3	25.4 [19.6]
Femoxetine	301	6	50.2 [17.7]	6	16.8 [5.5]	5	22.7 [6.3]
Fluoxetine	304	6	50.7 [32.5]	6	13.5 [5.9]	6	22.0 [16.7]
Fluvoxamine	64	1	64	1	12	1	15.6
Venlafaxine	241	3	80.3 [22.8]	3	11.3 [1.2]	3	27.4 [3.7]
Mianserin	38	1	38	1	16	1	10.5
Captopril	12	1	12	1	68.0 [0.0]	Not reported	Not reported
Lisinopril	60	1	60	1	7.5	1	22
Candesartan	60	1	60	1	32	1	5
Telmisartan	84	1	84	1	12	1	17
Nifedipine	36	1	36	1	8	1	22
Nimodipine	426	6	71.0 [61.6]	6	17.7 [5.4]	5	16.8 [12.7]
Verapamil	43	2	21.5 [2.1]	2	22.0 [2.8]	2	34.0 [19.8]
Nicardipine	30	1	30	1	16	1	14
Clonidine	674	14	48.1 [32.9]	14	22.3 [12.2]	10	22.5 [11.5]
Guanfacine	37	1	37	1	12	1	8
Dihydroergocryptine	172	3	57.3 [39.0]	3	28.0 [12.0]	Not reported	Not reported
Dihydroergotamine	605	4	151.3 [156.9]	4	10.5 [6.4]	4	3.9 [7.1]

Appendix Table D4. Total sample, weeks of followup, and percentage of loss of followup in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Drug	Total Sample	# RCTs	Mean [Standard Deviation]	# RCTs	Weeks of Followup Mean [Standard Deviation]	# RCTs	% Loss of Followup Mean [Standard Deviation]
Lisuride	343	3	114.3 [64.4]	3	15.3 [5.8]	2	13.9 [19.6]
Methysergide	92	2	46.0 [39.6]	2	17.0 [9.9]	2	24.6 [11.1]
Non -drug	632	4	158.0 [44.2]	4	20.0 [4.6]	Not reported	
Aspirin	23315	5	4663.0 [9739.6]	5	50.4 [56.0]	4	17.3 [12.8]
Fenoprofen	110	1	110	1	12	1	6.8
Flurbiprofen	29	1	29	1	20.0 [0.0]	Not reported	Not reported
Indobufen	28	1	28	1	12.0 [0.0]	Not reported	Not reported
Indomethacin	38	1	38	1	4.0 [0.0]	Not reported	Not reported
Induprofen	40	1	40	1	12.0 [0.0]	Not reported	Not reported
Ketoprofen	26	1	26	1	12.0 [0.0]	Not reported	Not reported
Naproxen sodium	101	3	33.7 [6.0]	3	16.7 [4.2]	1	15
Rofecoxib	268	1	268	1	20.0 [0.0]	Not reported	Not reported
Tolfenamic Acid	38	1	38	1	22.0 [0.0]	Not reported	Not reported
Magnesium	174	3	58.0 [30.0]	3	17.3 [6.1]	3	23.0 [16.6]
Montelukast	177	1	177	1	20	1	2.2
Tizanidine	136	1	136	1	12.0 [0.0]	Not reported	Not reported
Tonabersat	124	1	124	1	13	1	5.1

* approved drugs; # RCTs- = number of randomized controlled clinical trials that reported the variable

Appendix Table D5. Reporting of baseline patient characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults

Drug	# RCTs	Age Mean [STD]	# RCTs	% Women Mean [STD]	# RCTs	Body Mass Index Mean [STD]	# RCTs	Years with Migraine Mean [STD]	# RCTs	Migraine Attacks/Month Mean [STD]	# RCTs	% with Aura Mean [STD]
Topiramate*	25	38.8 [3.9]	25	77.6 [18.1]	5	28.3 [1.7]	9	9.3 [5.5]	24	8.0 [5.5]	8	16.3 [16.1]
Divalproex*	3	42.3 [2.9]	3	81.9 [6.2]	1	26.7	3	22.3 [2.5]	3	2.9 [2.5]	2	4.0 [1.4]
Propranolol*	35	37.6 [3.6]	41	77.7 [7.9]	Not reported	Not reported	19	16.3 [3.8]	27	4.9 [1.4]	31	44.8 [35.9]
Timolol*	1	43	2	71.7 [0.4]	Not reported	Not reported	Not reported	Not reported	2	3.9[2.6]	2	9.5 [6.8]
Acetazolamide	1	39.2	1	75.5	1	23	Not reported		1	5	1	9.4
Gabapentin	3	40.6 [2.1]	4	60.5 [32.5]	1	25.6	1	20.8	4	4.5 [1.0]	2	46.5 [3.9]
Lamotrigine	1	37.2	1	81.8	Not reported	Not reported	Not reported	Not reported	1	4	1	40.3
Oxcarbazepine	1	40.5	1	84.7	Not reported	Not reported	Not reported	Not reported	1	6	Not reported	
Valproate	4	37.5 [5.7]	4	79.2 [6.5]	Not reported	Not reported	1	14	4	5.6 [1.5]	3	35.9 [44.9]
Vigabatrin	1	43.6	1	73.9	Not reported	Not reported	Not reported	Not reported	1	2	1	43.5
Carbamazepine	Not reported		1	68.8	Not reported	Not reported	Not reported	Not reported	1	3	Not reported	
Alprenolol	1	41.3	1	81.8	Not reported	Not reported	Not reported	Not reported	1	3	1	18.2
Atenolol	2	41.5 [2.1]	2	74.9 [7.2]	Not reported	Not reported	1	26	1	2	2	0.0 [0.0]
Bisoprolol	1	38.7	1	82	1	23.4	Not reported	Not reported	1	5.5	1	23
Metoprolol	7	37.3 [3.3]	9	82.0 [2.9]	1	22.8	7	16.8 [3.9]	8	4.2 [1.4]	6	39.2 [46.7]
Nadolol	1	36.3	2	79.4 [2.7]	Not reported	Not reported	Not reported	Not reported	1	3	1	84.4
Pindolol	2	34.8 [1.5]	2	86.2 [0.7]	Not reported	Not reported	Not reported	Not reported	2	3.0 [1.4]	2	31.7 [25.9]
Acebutolol	Not reported		1	74.4	Not reported	Not reported	Not reported	Not reported	1	4.8	Not reported	0.0 [0.0]
Amitriptyline	2	33.5 [2.1]	4	80.7 [5.4]	Not reported	Not reported	1	16		0.0 [0.0]	1	24

Appendix Table D5. Reporting of baseline patient characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Drug	# RCTs	Age Mean [STD]	# RCTs	% Women Mean [STD]	# RCTs	Body Mass Index Mean [STD]	# RCTs	Years with Migraine Mean [STD]	# RCTs	Migraine Attacks/Month Mean [STD]	# RCTs	% with Aura Mean [STD]
Femoxetine	5	40.3 [2.6]	5	79.9 [8.8]	Not reported	Not reported	1	20.8	1	5	1	36.5
Fluoxetine	6	36.6 [3.1]	6	76.1 [9.4]	Not reported	Not reported	Not reported	Not reported	1	7	2	22.6 [32.0]
Fluvoxamine	1	34	1	73.4	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	1	18.8
Venlafaxine	3	33.8 [3.8]	3	85.4 [4.2]	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	3	9.8 [11.9]
Mianserin	Not reported		Not reported	Not reported [0.0]	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	
Captopril	1	49	1	58	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	
Lisinopril	1	41	1	81	Not reported	Not reported	Not reported	Not reported	1	2.3	Not reported	
Candesartan	1	42	1	79	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	
Telmisartan	1	39.8	1	84.5	1	24	Not reported	Not reported	1	6.2	Not reported	
Nifedipine	1	29.8	1	79	Not reported	Not reported	1	8.8	1	10	Not reported	
Nimodipine	5	37.5 [4.5]	5	64.8 [11.6]	1	23	3	18.7 [1.9]	3	5.0 [1.3]	3	21.6 [28.9]
Verapamil	2	36.0 [4.2]	2	80.5 [7.8]	Not reported	Not reported	1	13.4	1	5.3	1	41.7
Nicardipine	Not reported	0.0 [0.0]	1	73	Not reported	Not reported	1	8	1	4.3	1	100
Clonidine	12	37.8 [5.1]	13	76.9 [16.0]	Not reported	Not reported	3	16.0 [5.3]	5	5.1 [1.1]	Not reported	
Guanfacine	Not reported		1	84	Not reported	Not reported	Not reported	Not reported	Not reported		Not reported	
Dihydroergocryptine	2	34.3 [0.5]	3	74.4 [2.6]	Not reported	Not reported	Not reported	Not reported	3	5.3 [0.9]	3	0.0 [0.0]
Dihydroergotamine	3	37.5 [1.4]	4	69.8 [8.5]	2	23.7 [0.8]	2	15.9 [0.1]	2	4.4 [1.6]	4	15.8 [31.6]
Lisuride	2	31.8 [2.5]	2	84.1 [15.4]	Not reported	Not reported	2	14.6 [0.6]	3	5.7 [2.5]	2	43.8 [33.6]

Appendix Table D5. Reporting of baseline patient characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults (continued)

Drug	# RCTs	Age Mean [STD]	# RCTs	% Women Mean [STD]	# RCTs	Body Mass Index Mean [STD]	# RCTs	Years with Migraine Mean [STD]	# RCTs	Migraine Attacks/Month Mean [STD]	# RCTs	% with Aura Mean [STD]
Methysergide	2	37.6 [6.2]	2	81.7 [2.3]	Not reported	Not reported	1	20	1	3	1	11.1
Non -drug	4	38.9 [1.2]	4	87.9 [8.9]	1	23.5	1	15.9	3	4.7 [2.4]	3	38.9 [53.6]
Aspirin	4	44.7 [8.8]	4	61.5 [43.1]	2	25.6 [0.8]	Not reported	0.0 [0.0]	2	7.2 [1.5]	Not reported	0.0 [0.0]
Fenoprofen	1	40.5	1	81	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported		Not reported	0.0 [0.0]
Flurbiprofen	1	36	1	80	Not reported	Not reported	1	17	Not reported		1	8.7
Indobufen	1	35	Not reported	Not reported [0.0]	Not reported	Not reported	Not reported	0.0 [0.0]	1	4.8	1	0
Indomethacin	1	40	1	76	Not reported	Not reported	1	20	Not reported		Not reported	Not reported
Induprofen	1	35.8	1	60	Not reported	Not reported	1	15	Not reported		Not reported	Not reported
Ketoprofen	1	36	1	88	Not reported	Not reported	Not reported	0.0 [0.0]	1	2.8	Not reported	Not reported
Naproxen sodium	3	38.8 [0.8]	3	79.3 [10.3]	Not reported	Not reported	1	16.6	1	1.3	Not reported	Not reported
Rofecoxib	1	39.7	1	84.5	Not reported	Not reported	Not reported	Not reported	1	5.2	Not reported	Not reported
Tolfenamic Acid	1	35	1	87	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	Not reported
Magnesium	2	42.4 [2.0]	2	89.5 [4.9]	Not reported	Not reported	1	4.2	2	5.0 [1.4]	2	50.0 [70.7]
Montelukast	1	40	1	88	Not reported	Not reported	Not reported	Not reported	1	5.1	Not reported	Not reported
Tizanidine	1	40.3	1	79	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	Not reported
Tonabersat	1	36	1	92.3	Not reported	Not reported	Not reported	Not reported	Not reported	0.0 [0.0]	Not reported	Not reported

STD = standard deviation; #RCTs = number of randomized controlled clinical trials that reported baseline variable;* approved drugs

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0)

Baseline Variable	Active drug class	Comparator	Difference in baseline variable (95% CI)
Age	Acetazolamide	Alprenolol	-2.1 (-14.4 to 10.2)
Age	Acetazolamide	Amitriptyline	4.3 (-8.0 to 16.6)
Age	Acetazolamide	Aspirin	-5.5 (-15.2 to 4.2)
Age	Acetazolamide	Atenolol	-2.3 (-12.9 to 8.3)
Age	Acetazolamide	Candesartan	-2.8 (-15.1 to 9.5)
Age	Acetazolamide	Captopril	-9.8 (-22.1 to 2.5)
Age	Acetazolamide	Clonidine	0.9 (-8.2 to 10.0)
Age	Acetazolamide	Dihydroergotamine	1.7 (-8.3 to 11.7)
Age	Acetazolamide	Divalproex	-3.9 (-14.5 to 6.8)
Age	Acetazolamide	Femoxetine	-0.8 (-10.8 to 9.2)
Age	Acetazolamide	Fluoxetine	1.1 (-8.6 to 10.8)
Age	Acetazolamide	Gabapentin	-2.1 (-12.7 to 8.5)
Age	Acetazolamide	Indobufen	4.2 (-8.1 to 16.5)
Age	Acetazolamide	Indomethacin	-0.8 (-13.1 to 11.5)
Age	Acetazolamide	Induprofen	3.5 (-8.8 to 15.7)
Age	Acetazolamide	Induprofen	3.2 (-9.1 to 15.5)
Age	Acetazolamide	Lamotrigine	2.0 (-10.3 to 14.3)
Age	Acetazolamide	Lisinopril	-1.8 (-14.1 to 10.5)
Age	Acetazolamide	Magnesium	-3.2 (-13.8 to 7.4)
Age	Acetazolamide	Methysergide	-2.8 (-15.1 to 9.5)
Age	Acetazolamide	Metoprolol	1.1 (-8.9 to 11.2)
Age	Acetazolamide	Montelukast	-0.8 (-13.1 to 11.5)
Age	Acetazolamide	Nadolol	2.9 (-9.4 to 15.2)
Age	Acetazolamide	Naproxen sodium	0.4 (-9.6 to 10.5)
Age	Acetazolamide	Nifedipine	9.4 (-2.9 to 21.7)
Age	Acetazolamide	Nimodipine	2.5 (-7.5 to 12.6)
Age	Acetazolamide	Oxcarbazepine	-1.3 (-13.6 to 11.0)
Age	Acetazolamide	Pindolol	3.4 (-8.9 to 15.7)
Age	Acetazolamide	Propranolol	-0.3 (-9.5 to 8.9)
Age	Acetazolamide	Rofecoxib	-0.5 (-12.8 to 11.8)
Age	Acetazolamide	Telmisartan	-0.6 (-12.9 to 11.7)
Age	Acetazolamide	Timolol	-3.8 (-16.1 to 8.5)
Age	Acetazolamide	Tizanidine	-1.1 (-13.4 to 11.2)
Age	Acetazolamide	Tolfenamic Acid	4.2 (-8.1 to 16.5)
Age	Acetazolamide	Tonabersat	3.2 (-9.1 to 15.5)
Age	Acetazolamide	Topiramate	-2.1 (-11.3 to 7.0)
Age	Acetazolamide	Valproate	-0.8 (-11.4 to 9.8)
Age	Acetazolamide	Verapamil	3.3 (-7.4 to 13.9)
Age	Acetazolamide	Vigabatrin	-4.4 (-16.7 to 7.9)
Age	Alprenolol	Amitriptyline	6.4 (-5.9 to 18.7)
Age	Alprenolol	Aspirin	-3.4 (-13.1 to 6.3)
Age	Alprenolol	Atenolol	-0.2 (-10.8 to 10.4)
Age	Alprenolol	Candesartan	-0.7 (-13.0 to 11.6)
Age	Alprenolol	Captopril	-7.7 (-20.0 to 4.6)
Age	Alprenolol	Clonidine	3.0 (-6.1 to 12.1)
Age	Alprenolol	Dihydroergotamine	3.8 (-6.2 to 13.8)
Age	Alprenolol	Divalproex	-1.8 (-12.4 to 8.9)
Age	Alprenolol	Femoxetine	1.3 (-8.7 to 11.3)
Age	Alprenolol	Fluoxetine	3.2 (-6.5 to 12.9)
Age	Alprenolol	Gabapentin	0.0 (-10.6 to 10.6)
Age	Alprenolol	Indobufen	6.3 (-6.0 to 18.6)
Age	Alprenolol	Indomethacin	1.3 (-11.0 to 13.6)
Age	Alprenolol	Induprofen	5.6 (-6.7 to 17.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Alprenolol	Induprofen	5.3 (-7.0 to 17.6)
Age	Alprenolol	Lamotrigine	4.1 (-8.2 to 16.4)
Age	Alprenolol	Lisinopril	0.3 (-12.0 to 12.6)
Age	Alprenolol	Magnesium	-1.1 (-11.7 to 9.5)
Age	Alprenolol	Methysergide	-0.7 (-13.0 to 11.6)
Age	Alprenolol	Metoprolol	3.2 (-6.8 to 13.3)
Age	Alprenolol	Montelukast	1.3 (-11.0 to 13.6)
Age	Alprenolol	Nadolol	5.0 (-7.3 to 17.3)
Age	Alprenolol	Naproxen sodium	2.5 (-7.5 to 12.6)
Age	Alprenolol	Nifedipine	11.5 (-0.8 to 23.8)
Age	Alprenolol	Nimodipine	4.6 (-5.4 to 14.7)
Age	Alprenolol	Oxcarbazepine	0.8 (-11.5 to 13.1)
Age	Alprenolol	Pindolol	5.5 (-6.8 to 17.8)
Age	Alprenolol	Propranolol	1.8 (-7.4 to 11.0)
Age	Alprenolol	Rofecoxib	1.6 (-10.7 to 13.9)
Age	Alprenolol	Telmisartan	1.5 (-10.8 to 13.8)
Age	Alprenolol	Timolol	-1.7 (-14.0 to 10.6)
Age	Alprenolol	Tizanidine	1.0 (-11.3 to 13.3)
Age	Alprenolol	Tolfenamic Acid	6.3 (-6.0 to 18.6)
Age	Alprenolol	Tonabersat	5.3 (-7.0 to 17.6)
Age	Alprenolol	Topiramate	0.0 (-9.2 to 9.1)
Age	Alprenolol	Valproate	1.3 (-9.3 to 11.9)
Age	Alprenolol	Verapamil	5.4 (-5.3 to 16.0)
Age	Alprenolol	Vigabatrin	-2.3 (-14.6 to 10.0)
Age	Amitriptyline	Aspirin	-9.8 (-19.5 to -0.1)
Age	Amitriptyline	Atenolol	-6.6 (-17.2 to 4.0)
Age	Amitriptyline	Candesartan	-7.1 (-19.4 to 5.2)
Age	Amitriptyline	Captopril	-14.1 (-26.4 to -1.8)
Age	Amitriptyline	Clonidine	-3.4 (-12.5 to 5.7)
Age	Amitriptyline	Dihydroergotamine	-2.6 (-12.6 to 7.4)
Age	Amitriptyline	Divalproex	-8.2 (-18.8 to 2.5)
Age	Amitriptyline	Femoxetine	-5.1 (-15.1 to 4.9)
Age	Amitriptyline	Fluoxetine	-3.2 (-12.9 to 6.5)
Age	Amitriptyline	Gabapentin	-6.4 (-17.0 to 4.2)
Age	Amitriptyline	Indobufen	-0.1 (-12.4 to 12.2)
Age	Amitriptyline	Indomethacin	-5.1 (-17.4 to 7.2)
Age	Amitriptyline	Induprofen	-0.9 (-13.1 to 11.4)
Age	Amitriptyline	Induprofen	-1.1 (-13.4 to 11.2)
Age	Amitriptyline	Lamotrigine	-2.3 (-14.6 to 10.0)
Age	Amitriptyline	Lisinopril	-6.1 (-18.4 to 6.2)
Age	Amitriptyline	Magnesium	-7.5 (-18.1 to 3.1)
Age	Amitriptyline	Methysergide	-7.1 (-19.4 to 5.2)
Age	Amitriptyline	Metoprolol	-3.2 (-13.2 to 6.9)
Age	Amitriptyline	Montelukast	-5.1 (-17.4 to 7.2)
Age	Amitriptyline	Nadolol	-1.4 (-13.7 to 10.9)
Age	Amitriptyline	Naproxen sodium	-3.9 (-13.9 to 6.2)
Age	Amitriptyline	Nifedipine	5.1 (-7.2 to 17.4)
Age	Amitriptyline	Nimodipine	-1.8 (-11.8 to 8.3)
Age	Amitriptyline	Oxcarbazepine	-5.6 (-17.9 to 6.7)
Age	Amitriptyline	Pindolol	-0.9 (-13.2 to 11.4)
Age	Amitriptyline	Propranolol	-4.6 (-13.8 to 4.6)
Age	Amitriptyline	Rofecoxib	-4.8 (-17.1 to 7.5)
Age	Amitriptyline	Telmisartan	-4.9 (-17.2 to 7.4)
Age	Amitriptyline	Timolol	-8.1 (-20.4 to 4.2)
Age	Amitriptyline	Tizanidine	-5.4 (-17.7 to 6.9)
Age	Amitriptyline	Tolfenamic Acid	-0.1 (-12.4 to 12.2)
Age	Amitriptyline	Tonabersat	-1.1 (-13.4 to 11.2)
Age	Amitriptyline	Topiramate	-6.4 (-15.6 to 2.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Amitriptyline	Valproate	-5.1 (-15.7 to 5.5)
Age	Amitriptyline	Verapamil	-1.1 (-11.7 to 9.6)
Age	Amitriptyline	Vigabatrin	-8.7 (-21.0 to 3.6)
Age	Aspirin	Atenolol	3.2 (-4.3 to 10.7)
Age	Aspirin	Candesartan	2.7 (-7.0 to 12.4)
Age	Aspirin	Captopril	-4.3 (-14.0 to 5.4)
Age	Aspirin	Clonidine	6.4 (1.4 to 11.5)
Age	Aspirin	Dihydroergotamine	7.2 (0.6 to 13.8)
Age	Aspirin	Divalproex	1.7 (-5.8 to 9.1)
Age	Aspirin	Femoxetine	4.7 (-1.9 to 11.3)
Age	Aspirin	Fluoxetine	6.6 (0.5 to 12.7)
Age	Aspirin	Gabapentin	3.4 (-4.1 to 10.9)
Age	Aspirin	Indobufen	9.7 (0.0 to 19.4)
Age	Aspirin	Indomethacin	4.7 (-5.0 to 14.4)
Age	Aspirin	Induprofen	9.0 (-0.7 to 18.6)
Age	Aspirin	Ketoprofen	8.7 (-1.0 to 18.4)
Age	Aspirin	Lamotrigine	7.5 (-2.2 to 17.2)
Age	Aspirin	Lisinopril	3.7 (-6.0 to 13.4)
Age	Aspirin	Methysergide	2.7 (-7.0 to 12.4)
Age	Aspirin	Metoprolol	6.6 (0.0 to 13.2)
Age	Aspirin	Magnesium	2.3 (-5.2 to 9.8)
Age	Aspirin	Montelukast	4.7 (-5.0 to 14.4)
Age	Aspirin	Nadolol	8.4 (-1.3 to 18.1)
Age	Aspirin	Naproxen sodium	5.9 (-0.7 to 12.5)
Age	Aspirin	Nifedipine	14.9 (5.2 to 24.6)
Age	Aspirin	Nimodipine	8.0 (1.4 to 14.6)
Age	Aspirin	Oxcarbazepine	4.2 (-5.5 to 13.9)
Age	Aspirin	Pindolol	8.9 (-0.8 to 18.6)
Age	Aspirin	Propranolol	5.2 (-0.1 to 10.5)
Age	Aspirin	Rofecoxib	5.0 (-4.7 to 14.7)
Age	Aspirin	Telmisartan	4.9 (-4.8 to 14.6)
Age	Aspirin	Timolol	1.7 (-8.0 to 11.4)
Age	Aspirin	Tizanidine	4.4 (-5.3 to 14.1)
Age	Aspirin	Tolfenamic Acid	9.7 (0.0 to 19.4)
Age	Aspirin	Tonabersat	8.7 (-1.0 to 18.4)
Age	Aspirin	Topiramate	3.4 (-1.8 to 8.6)
Age	Aspirin	Valproate	4.7 (-2.8 to 12.2)
Age	Aspirin	Verapamil	8.8 (1.3 to 16.2)
Age	Aspirin	Vigabatrin	1.1 (-8.6 to 10.8)
Age	Atenolol	Candesartan	-0.5 (-11.1 to 10.1)
Age	Atenolol	Captopril	-7.5 (-18.1 to 3.1)
Age	Atenolol	Clonidine	3.2 (-3.5 to 9.9)
Age	Atenolol	Dihydroergotamine	4.0 (-3.9 to 11.9)
Age	Atenolol	Divalproex	-1.6 (-10.2 to 7.1)
Age	Atenolol	Femoxetine	1.5 (-6.4 to 9.4)
Age	Atenolol	Fluoxetine	3.4 (-4.1 to 10.9)
Age	Atenolol	Gabapentin	0.2 (-8.5 to 8.9)
Age	Atenolol	Indobufen	6.5 (-4.1 to 17.1)
Age	Atenolol	Indomethacin	1.5 (-9.1 to 12.1)
Age	Atenolol	Induprofen	5.8 (-4.9 to 16.4)
Age	Atenolol	Induprofen	5.5 (-5.1 to 16.1)
Age	Atenolol	Lamotrigine	4.3 (-6.3 to 14.9)
Age	Atenolol	Lisinopril	0.5 (-10.1 to 11.1)
Age	Atenolol	Magnesium	-0.9 (-9.6 to 7.8)
Age	Atenolol	Methysergide	-0.5 (-11.1 to 10.1)
Age	Atenolol	Metoprolol	3.4 (-4.5 to 11.4)
Age	Atenolol	Montelukast	1.5 (-9.1 to 12.1)
Age	Atenolol	Nadolol	5.2 (-5.4 to 15.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Atenolol	Naproxen sodium	2.7 (-5.2 to 10.7)
Age	Atenolol	Nifedipine	11.7 (1.1 to 22.3)
Age	Atenolol	Nimodipine	4.8 (-3.1 to 12.8)
Age	Atenolol	Oxcarbazepine	1.0 (-9.6 to 11.6)
Age	Atenolol	Pindolol	5.7 (-4.9 to 16.3)
Age	Atenolol	Propranolol	2.0 (-4.8 to 8.9)
Age	Atenolol	Rofecoxib	1.8 (-8.8 to 12.4)
Age	Atenolol	Telmisartan	1.7 (-8.9 to 12.3)
Age	Atenolol	Timolol	-1.5 (-12.1 to 9.1)
Age	Atenolol	Tizanidine	1.2 (-9.4 to 11.8)
Age	Atenolol	Tolfenamic Acid	6.5 (-4.1 to 17.1)
Age	Atenolol	Tonabersat	5.5 (-5.1 to 16.1)
Age	Atenolol	Topiramate	0.2 (-6.6 to 7.0)
Age	Atenolol	Valproate	1.5 (-7.2 to 10.2)
Age	Atenolol	Verapamil	5.6 (-3.1 to 14.2)
Age	Atenolol	Vigabatrin	-2.1 (-12.7 to 8.5)
Age	Candesartan	Captopril	-7.0 (-19.3 to 5.3)
Age	Candesartan	Clonidine	3.7 (-5.4 to 12.8)
Age	Candesartan	Dihydroergotamine	4.5 (-5.5 to 14.5)
Age	Candesartan	Divalproex	-1.1 (-11.7 to 9.6)
Age	Candesartan	Femoxetine	2.0 (-8.0 to 12.0)
Age	Candesartan	Fluoxetine	3.9 (-5.8 to 13.6)
Age	Candesartan	Gabapentin	0.7 (-9.9 to 11.3)
Age	Candesartan	Indobufen	7.0 (-5.3 to 19.3)
Age	Candesartan	Indomethacin	2.0 (-10.3 to 14.3)
Age	Candesartan	Induprofen	6.3 (-6.0 to 18.5)
Age	Candesartan	Induprofen	6.0 (-6.3 to 18.3)
Age	Candesartan	Lamotrigine	4.8 (-7.5 to 17.1)
Age	Candesartan	Lisinopril	1.0 (-11.3 to 13.3)
Age	Candesartan	Magnesium	-0.4 (-11.0 to 10.2)
Age	Candesartan	Methysergide	0.0 (-12.3 to 12.3)
Age	Candesartan	Metoprolol	3.9 (-6.1 to 14.0)
Age	Candesartan	Montelukast	2.0 (-10.3 to 14.3)
Age	Candesartan	Nadolol	5.7 (-6.6 to 18.0)
Age	Candesartan	Naproxen sodium	3.2 (-6.8 to 13.3)
Age	Candesartan	Nifedipine	12.2 (-0.1 to 24.5)
Age	Candesartan	Nimodipine	5.3 (-4.7 to 15.4)
Age	Candesartan	Oxcarbazepine	1.5 (-10.8 to 13.8)
Age	Candesartan	Pindolol	6.2 (-6.1 to 18.5)
Age	Candesartan	Propranolol	2.5 (-6.7 to 11.7)
Age	Candesartan	Rofecoxib	2.3 (-10.0 to 14.6)
Age	Candesartan	Telmisartan	2.2 (-10.1 to 14.5)
Age	Candesartan	Timolol	-1.0 (-13.3 to 11.3)
Age	Candesartan	Tizanidine	1.7 (-10.6 to 14.0)
Age	Candesartan	Tolfenamic Acid	7.0 (-5.3 to 19.3)
Age	Candesartan	Tonabersat	6.0 (-6.3 to 18.3)
Age	Candesartan	Topiramate	0.7 (-8.5 to 9.8)
Age	Candesartan	Valproate	2.0 (-8.6 to 12.6)
Age	Candesartan	Verapamil	6.1 (-4.6 to 16.7)
Age	Candesartan	Vigabatrin	-1.6 (-13.9 to 10.7)
Age	Captopril	Clonidine	10.7 (1.6 to 19.8)
Age	Captopril	Dihydroergotamine	11.5 (1.5 to 21.5)
Age	Captopril	Divalproex	6.0 (-4.7 to 16.6)
Age	Captopril	Femoxetine	9.0 (-1.0 to 19.0)
Age	Captopril	Fluoxetine	10.9 (1.2 to 20.6)
Age	Captopril	Gabapentin	7.7 (-2.9 to 18.3)
Age	Captopril	Indobufen	14.0 (1.7 to 26.3)
Age	Captopril	Indomethacin	9.0 (-3.3 to 21.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Captopril	Induprofen	13.3 (1.0 to 25.5)
Age	Captopril	Induprofen	13.0 (0.7 to 25.3)
Age	Captopril	Lamotrigine	11.8 (-0.5 to 24.1)
Age	Captopril	Lisinopril	8.0 (-4.3 to 20.3)
Age	Captopril	Magnesium	6.6 (-4.0 to 17.2)
Age	Captopril	Methysergide	7.0 (-5.3 to 19.3)
Age	Captopril	Metoprolol	10.9 (0.9 to 21.0)
Age	Captopril	Montelukast	9.0 (-3.3 to 21.3)
Age	Captopril	Nadolol	12.7 (0.4 to 25.0)
Age	Captopril	Naproxen sodium	10.2 (0.2 to 20.3)
Age	Captopril	Nifedipine	19.2 (6.9 to 31.5)
Age	Captopril	Nimodipine	12.3 (2.3 to 22.4)
Age	Captopril	Oxcarbazepine	8.5 (-3.8 to 20.8)
Age	Captopril	Pindolol	13.2 (0.9 to 25.5)
Age	Captopril	Propranolol	9.5 (0.3 to 18.7)
Age	Captopril	Rofecoxib	9.3 (-3.0 to 21.6)
Age	Captopril	Telmisartan	9.2 (-3.1 to 21.5)
Age	Captopril	Timolol	6.0 (-6.3 to 18.3)
Age	Captopril	Tizanidine	8.7 (-3.6 to 21.0)
Age	Captopril	Tolfenamic Acid	14.0 (1.7 to 26.3)
Age	Captopril	Tonabersat	13.0 (0.7 to 25.3)
Age	Captopril	Topiramate	7.7 (-1.5 to 16.8)
Age	Captopril	Valproate	9.0 (-1.6 to 19.6)
Age	Captopril	Verapamil	13.1 (2.4 to 23.7)
Age	Captopril	Vigabatrin	5.4 (-6.9 to 17.7)
Age	Clonidine	Dihydroergotamine	0.8 (-4.9 to 6.4)
Age	Clonidine	Divalproex	-4.8 (-11.4 to 1.9)
Age	Clonidine	Femoxetine	-1.7 (-7.4 to 3.9)
Age	Clonidine	Fluoxetine	0.2 (-4.9 to 5.3)
Age	Clonidine	Gabapentin	-3.0 (-9.7 to 3.7)
Age	Clonidine	Indobufen	3.3 (-5.8 to 12.4)
Age	Clonidine	Indomethacin	-1.7 (-10.8 to 7.4)
Age	Clonidine	Induprofen	2.5 (-6.5 to 11.6)
Age	Clonidine	Induprofen	2.3 (-6.8 to 11.4)
Age	Clonidine	Lamotrigine	1.1 (-8.0 to 10.2)
Age	Clonidine	Lisinopril	-2.7 (-11.8 to 6.4)
Age	Clonidine	Magnesium	-4.1 (-10.8 to 2.6)
Age	Clonidine	Methysergide	-3.7 (-12.8 to 5.4)
Age	Clonidine	Metoprolol	0.2 (-5.4 to 5.9)
Age	Clonidine	Montelukast	-1.7 (-10.8 to 7.4)
Age	Clonidine	Nadolol	2.0 (-7.1 to 11.1)
Age	Clonidine	Naproxen sodium	-0.5 (-6.1 to 5.2)
Age	Clonidine	Nifedipine	8.5 (-0.6 to 17.6)
Age	Clonidine	Nimodipine	1.6 (-4.0 to 7.3)
Age	Clonidine	Oxcarbazepine	-2.2 (-11.3 to 6.9)
Age	Clonidine	Pindolol	2.5 (-6.6 to 11.6)
Age	Clonidine	Propranolol	-1.2 (-5.2 to 2.8)
Age	Clonidine	Rofecoxib	-1.4 (-10.5 to 7.7)
Age	Clonidine	Telmisartan	-1.5 (-10.6 to 7.6)
Age	Clonidine	Timolol	-4.7 (-13.8 to 4.4)
Age	Clonidine	Tizanidine	-2.0 (-11.1 to 7.1)
Age	Clonidine	Tolfenamic Acid	3.3 (-5.8 to 12.4)
Age	Clonidine	Tonabersat	2.3 (-6.8 to 11.4)
Age	Clonidine	Topiramate	-3.0 (-6.9 to 0.9)
Age	Clonidine	Valproate	-1.7 (-8.4 to 5.0)
Age	Clonidine	Verapamil	2.3 (-4.3 to 9.0)
Age	Clonidine	Vigabatrin	-5.3 (-14.4 to 3.8)
Age	Dihydroergotamine	Divalproex	-5.6 (-13.5 to 2.4)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Dihydroergotamine	Femoxetine	-2.5 (-9.6 to 4.6)
Age	Dihydroergotamine	Fluoxetine	-0.6 (-7.2 to 6.1)
Age	Dihydroergotamine	Gabapentin	-3.8 (-11.7 to 4.1)
Age	Dihydroergotamine	Indobufen	2.5 (-7.5 to 12.5)
Age	Dihydroergotamine	Indomethacin	-2.5 (-12.5 to 7.5)
Age	Dihydroergotamine	Induprofen	1.8 (-8.3 to 11.8)
Age	Dihydroergotamine	Induprofen	1.5 (-8.5 to 11.5)
Age	Dihydroergotamine	Lamotrigine	0.3 (-9.7 to 10.3)
Age	Dihydroergotamine	Lisinopril	-3.5 (-13.5 to 6.5)
Age	Dihydroergotamine	Magnesium	-4.9 (-12.8 to 3.0)
Age	Dihydroergotamine	Methysergide	-4.5 (-14.5 to 5.5)
Age	Dihydroergotamine	Metoprolol	-0.6 (-7.7 to 6.5)
Age	Dihydroergotamine	Montelukast	-2.5 (-12.5 to 7.5)
Age	Dihydroergotamine	Nadolol	1.2 (-8.8 to 11.2)
Age	Dihydroergotamine	Naproxen sodium	-1.3 (-8.4 to 5.8)
Age	Dihydroergotamine	Nifedipine	7.7 (-2.3 to 17.7)
Age	Dihydroergotamine	Nimodipine	0.8 (-6.3 to 7.9)
Age	Dihydroergotamine	Oxcarbazepine	-3.0 (-13.0 to 7.0)
Age	Dihydroergotamine	Pindolol	1.7 (-8.3 to 11.7)
Age	Dihydroergotamine	Propranolol	-2.0 (-7.9 to 3.9)
Age	Dihydroergotamine	Rofecoxib	-2.2 (-12.2 to 7.8)
Age	Dihydroergotamine	Telmisartan	-2.3 (-12.3 to 7.7)
Age	Dihydroergotamine	Timolol	-5.5 (-15.5 to 4.5)
Age	Dihydroergotamine	Tizanidine	-2.8 (-12.8 to 7.2)
Age	Dihydroergotamine	Tolfenamic Acid	2.5 (-7.5 to 12.5)
Age	Dihydroergotamine	Tonabersat	1.5 (-8.5 to 11.5)
Age	Dihydroergotamine	Topiramate	-3.8 (-9.6 to 2.0)
Age	Dihydroergotamine	Valproate	-2.5 (-10.4 to 5.4)
Age	Dihydroergotamine	Verapamil	1.6 (-6.4 to 9.5)
Age	Dihydroergotamine	Vigabatrin	-6.1 (-16.1 to 3.9)
Age	Divalproex	Femoxetine	3.1 (-4.9 to 11.0)
Age	Divalproex	Fluoxetine	5.0 (-2.5 to 12.5)
Age	Divalproex	Gabapentin	1.8 (-6.9 to 10.4)
Age	Divalproex	Indobufen	8.1 (-2.6 to 18.7)
Age	Divalproex	Indomethacin	3.1 (-7.6 to 13.7)
Age	Divalproex	Induprofen	7.3 (-3.3 to 17.9)
Age	Divalproex	Induprofen	7.1 (-3.6 to 17.7)
Age	Divalproex	Lamotrigine	5.9 (-4.8 to 16.5)
Age	Divalproex	Lisinopril	2.1 (-8.6 to 12.7)
Age	Divalproex	Magnesium	0.7 (-8.0 to 9.3)
Age	Divalproex	Methysergide	1.1 (-9.6 to 11.7)
Age	Divalproex	Metoprolol	5.0 (-2.9 to 12.9)
Age	Divalproex	Montelukast	3.1 (-7.6 to 13.7)
Age	Divalproex	Nadolol	6.8 (-3.9 to 17.4)
Age	Divalproex	Naproxen sodium	4.3 (-3.6 to 12.2)
Age	Divalproex	Nifedipine	13.3 (2.6 to 23.9)
Age	Divalproex	Nimodipine	6.4 (-1.5 to 14.3)
Age	Divalproex	Oxcarbazepine	2.6 (-8.1 to 13.2)
Age	Divalproex	Pindolol	7.3 (-3.4 to 17.9)
Age	Divalproex	Propranolol	3.6 (-3.3 to 10.4)
Age	Divalproex	Rofecoxib	3.4 (-7.3 to 14.0)
Age	Divalproex	Telmisartan	3.3 (-7.4 to 13.9)
Age	Divalproex	Timolol	0.1 (-10.6 to 10.7)
Age	Divalproex	Tizanidine	2.8 (-7.9 to 13.4)
Age	Divalproex	Tolfenamic Acid	8.1 (-2.6 to 18.7)
Age	Divalproex	Tonabersat	7.1 (-3.6 to 17.7)
Age	Divalproex	Topiramate	1.7 (-5.1 to 8.5)
Age	Divalproex	Valproate	3.1 (-5.6 to 11.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Divalproex	Verapamil	7.1 (-1.6 to 15.8)
Age	Divalproex	Vigabatrin	-0.6 (-11.2 to 10.1)
Age	Femoxetine	Fluoxetine	1.9 (-4.7 to 8.6)
Age	Femoxetine	Gabapentin	-1.3 (-9.2 to 6.6)
Age	Femoxetine	Indobufen	5.0 (-5.0 to 15.0)
Age	Femoxetine	Indomethacin	0.0 (-10.0 to 10.0)
Age	Femoxetine	Induprofen	4.3 (-5.8 to 14.3)
Age	Femoxetine	Induprofen	4.0 (-6.0 to 14.0)
Age	Femoxetine	Lamotrigine	2.8 (-7.2 to 12.8)
Age	Femoxetine	Lisinopril	-1.0 (-11.0 to 9.0)
Age	Femoxetine	Magnesium	-2.4 (-10.3 to 5.5)
Age	Femoxetine	Methysergide	-2.0 (-12.0 to 8.0)
Age	Femoxetine	Metoprolol	1.9 (-5.2 to 9.0)
Age	Femoxetine	Montelukast	0.0 (-10.0 to 10.0)
Age	Femoxetine	Nadolol	3.7 (-6.3 to 13.7)
Age	Femoxetine	Naproxen sodium	1.2 (-5.9 to 8.3)
Age	Femoxetine	Nifedipine	10.2 (0.2 to 20.2)
Age	Femoxetine	Nimodipine	3.3 (-3.8 to 10.4)
Age	Femoxetine	Oxcarbazepine	-0.5 (-10.5 to 9.5)
Age	Femoxetine	Pindolol	4.2 (-5.8 to 14.2)
Age	Femoxetine	Propranolol	0.5 (-5.4 to 6.4)
Age	Femoxetine	Rofecoxib	0.3 (-9.7 to 10.3)
Age	Femoxetine	Telmisartan	0.2 (-9.8 to 10.2)
Age	Femoxetine	Timolol	-3.0 (-13.0 to 7.0)
Age	Femoxetine	Tizanidine	-0.3 (-10.3 to 9.7)
Age	Femoxetine	Tolfenamic Acid	5.0 (-5.0 to 15.0)
Age	Femoxetine	Tonabersat	4.0 (-6.0 to 14.0)
Age	Femoxetine	Topiramate	-1.3 (-7.1 to 4.5)
Age	Femoxetine	Valproate	0.0 (-7.9 to 7.9)
Age	Femoxetine	Verapamil	4.1 (-3.9 to 12.0)
Age	Femoxetine	Vigabatrin	-3.6 (-13.6 to 6.4)
Age	Fluoxetine	Gabapentin	-3.2 (-10.7 to 4.3)
Age	Fluoxetine	Indobufen	3.1 (-6.6 to 12.8)
Age	Fluoxetine	Indomethacin	-1.9 (-11.6 to 7.8)
Age	Fluoxetine	Induprofen	2.3 (-7.4 to 12.0)
Age	Fluoxetine	Induprofen	2.1 (-7.6 to 11.8)
Age	Fluoxetine	Lamotrigine	0.9 (-8.8 to 10.6)
Age	Fluoxetine	Lisinopril	-2.9 (-12.6 to 6.8)
Age	Fluoxetine	Magnesium	-4.3 (-11.8 to 3.2)
Age	Fluoxetine	Methysergide	-3.9 (-13.6 to 5.8)
Age	Fluoxetine	Metoprolol	0.0 (-6.6 to 6.6)
Age	Fluoxetine	Montelukast	-1.9 (-11.6 to 7.8)
Age	Fluoxetine	Nadolol	1.8 (-7.9 to 11.5)
Age	Fluoxetine	Naproxen sodium	-0.7 (-7.3 to 5.9)
Age	Fluoxetine	Nifedipine	8.3 (-1.4 to 18.0)
Age	Fluoxetine	Nimodipine	1.4 (-5.2 to 8.0)
Age	Fluoxetine	Oxcarbazepine	-2.4 (-12.1 to 7.3)
Age	Fluoxetine	Pindolol	2.3 (-7.4 to 12.0)
Age	Fluoxetine	Propranolol	-1.4 (-6.7 to 3.9)
Age	Fluoxetine	Rofecoxib	-1.6 (-11.3 to 8.1)
Age	Fluoxetine	Telmisartan	-1.7 (-11.4 to 8.0)
Age	Fluoxetine	Timolol	-4.9 (-14.6 to 4.8)
Age	Fluoxetine	Tizanidine	-2.2 (-11.9 to 7.5)
Age	Fluoxetine	Tolfenamic Acid	3.1 (-6.6 to 12.8)
Age	Fluoxetine	Tonabersat	2.1 (-7.6 to 11.8)
Age	Fluoxetine	Topiramate	-3.2 (-8.5 to 2.0)
Age	Fluoxetine	Valproate	-1.9 (-9.4 to 5.6)
Age	Fluoxetine	Verapamil	2.1 (-5.4 to 9.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Fluoxetine	Vigabatrin	-5.5 (-15.2 to 4.2)
Age	Gabapentin	Indobufen	6.3 (-4.3 to 16.9)
Age	Gabapentin	Indomethacin	1.3 (-9.3 to 11.9)
Age	Gabapentin	Induprofen	5.6 (-5.1 to 16.2)
Age	Gabapentin	Induprofen	5.3 (-5.3 to 15.9)
Age	Gabapentin	Lamotrigine	4.1 (-6.5 to 14.7)
Age	Gabapentin	Lisinopril	0.3 (-10.3 to 10.9)
Age	Gabapentin	Magnesium	-1.1 (-9.8 to 7.6)
Age	Gabapentin	Methysergide	-0.7 (-11.3 to 9.9)
Age	Gabapentin	Metoprolol	3.2 (-4.7 to 11.2)
Age	Gabapentin	Montelukast	1.3 (-9.3 to 11.9)
Age	Gabapentin	Nadolol	5.0 (-5.6 to 15.6)
Age	Gabapentin	Naproxen sodium	2.5 (-5.4 to 10.5)
Age	Gabapentin	Nifedipine	11.5 (0.9 to 22.1)
Age	Gabapentin	Nimodipine	4.6 (-3.3 to 12.6)
Age	Gabapentin	Oxcarbazepine	0.8 (-9.8 to 11.4)
Age	Gabapentin	Pindolol	5.5 (-5.1 to 16.1)
Age	Gabapentin	Propranolol	1.8 (-5.0 to 8.7)
Age	Gabapentin	Rofecoxib	1.6 (-9.0 to 12.2)
Age	Gabapentin	Telmisartan	1.5 (-9.1 to 12.1)
Age	Gabapentin	Timolol	-1.7 (-12.3 to 8.9)
Age	Gabapentin	Tizanidine	1.0 (-9.6 to 11.6)
Age	Gabapentin	Tolfenamic Acid	6.3 (-4.3 to 16.9)
Age	Gabapentin	Tonabersat	5.3 (-5.3 to 15.9)
Age	Gabapentin	Topiramate	0.0 (-6.8 to 6.8)
Age	Gabapentin	Valproate	1.3 (-7.4 to 10.0)
Age	Gabapentin	Verapamil	5.4 (-3.3 to 14.0)
Age	Gabapentin	Vigabatrin	-2.3 (-12.9 to 8.3)
Age	Indobufen	Indomethacin	-5.0 (-17.3 to 7.3)
Age	Indobufen	Induprofen	-0.8 (-13.0 to 11.5)
Age	Indobufen	Induprofen	-1.0 (-13.3 to 11.3)
Age	Indobufen	Lamotrigine	-2.2 (-14.5 to 10.1)
Age	Indobufen	Lisinopril	-6.0 (-18.3 to 6.3)
Age	Indobufen	Magnesium	-7.4 (-18.0 to 3.2)
Age	Indobufen	Methysergide	-7.0 (-19.3 to 5.3)
Age	Indobufen	Metoprolol	-3.1 (-13.1 to 7.0)
Age	Indobufen	Montelukast	-5.0 (-17.3 to 7.3)
Age	Indobufen	Nadolol	-1.3 (-13.6 to 11.0)
Age	Indobufen	Naproxen sodium	-3.8 (-13.8 to 6.3)
Age	Indobufen	Nifedipine	5.2 (-7.1 to 17.5)
Age	Indobufen	Nimodipine	-1.7 (-11.7 to 8.4)
Age	Indobufen	Oxcarbazepine	-5.5 (-17.8 to 6.8)
Age	Indobufen	Pindolol	-0.8 (-13.1 to 11.5)
Age	Indobufen	Propranolol	-4.5 (-13.7 to 4.7)
Age	Indobufen	Rofecoxib	-4.7 (-17.0 to 7.6)
Age	Indobufen	Telmisartan	-4.8 (-17.1 to 7.5)
Age	Indobufen	Timolol	-8.0 (-20.3 to 4.3)
Age	Indobufen	Tizanidine	-5.3 (-17.6 to 7.0)
Age	Indobufen	Tolfenamic Acid	0.0 (-12.3 to 12.3)
Age	Indobufen	Tonabersat	-1.0 (-13.3 to 11.3)
Age	Indobufen	Topiramate	-6.3 (-15.5 to 2.8)
Age	Indobufen	Valproate	-5.0 (-15.6 to 5.6)
Age	Indobufen	Verapamil	-1.0 (-11.6 to 9.7)
Age	Indobufen	Vigabatrin	-8.6 (-20.9 to 3.7)
Age	Indomethacin	Induprofen	4.3 (-8.0 to 16.5)
Age	Indomethacin	Induprofen	4.0 (-8.3 to 16.3)
Age	Indomethacin	Lamotrigine	2.8 (-9.5 to 15.1)
Age	Indomethacin	Lisinopril	-1.0 (-13.3 to 11.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Indomethacin	Magnesium	-2.4 (-13.0 to 8.2)
Age	Indomethacin	Methysergide	-2.0 (-14.3 to 10.3)
Age	Indomethacin	Metoprolol	1.9 (-8.1 to 12.0)
Age	Indomethacin	Montelukast	0.0 (-12.3 to 12.3)
Age	Indomethacin	Nadolol	3.7 (-8.6 to 16.0)
Age	Indomethacin	Naproxen sodium	1.2 (-8.8 to 11.3)
Age	Indomethacin	Nifedipine	10.2 (-2.1 to 22.5)
Age	Indomethacin	Nimodipine	3.3 (-6.7 to 13.4)
Age	Indomethacin	Oxcarbazepine	-0.5 (-12.8 to 11.8)
Age	Indomethacin	Pindolol	4.2 (-8.1 to 16.5)
Age	Indomethacin	Propranolol	0.5 (-8.7 to 9.7)
Age	Indomethacin	Rofecoxib	0.3 (-12.0 to 12.6)
Age	Indomethacin	Telmisartan	0.2 (-12.1 to 12.5)
Age	Indomethacin	Timolol	-3.0 (-15.3 to 9.3)
Age	Indomethacin	Tizanidine	-0.3 (-12.6 to 12.0)
Age	Indomethacin	Tolfenamic Acid	5.0 (-7.3 to 17.3)
Age	Indomethacin	Tonabersat	4.0 (-8.3 to 16.3)
Age	Indomethacin	Topiramate	-1.3 (-10.5 to 7.8)
Age	Indomethacin	Valproate	0.0 (-10.6 to 10.6)
Age	Indomethacin	Verapamil	4.1 (-6.6 to 14.7)
Age	Indomethacin	Vigabatrin	-3.6 (-15.9 to 8.7)
Age	Induprofen	Induprofen	-0.3 (-12.5 to 12.0)
Age	Induprofen	Lamotrigine	-1.5 (-13.7 to 10.8)
Age	Induprofen	Lisinopril	-5.3 (-17.5 to 7.0)
Age	Induprofen	Magnesium	-6.7 (-17.3 to 4.0)
Age	Induprofen	Methysergide	-6.3 (-18.5 to 6.0)
Age	Induprofen	Metoprolol	-2.3 (-12.3 to 7.7)
Age	Induprofen	Montelukast	-4.3 (-16.5 to 8.0)
Age	Induprofen	Nadolol	-0.6 (-12.8 to 11.7)
Age	Induprofen	Naproxen sodium	-3.0 (-13.0 to 7.0)
Age	Induprofen	Nifedipine	6.0 (-6.3 to 18.2)
Age	Induprofen	Nimodipine	-0.9 (-10.9 to 9.1)
Age	Induprofen	Oxcarbazepine	-4.8 (-17.0 to 7.5)
Age	Induprofen	Pindolol	-0.1 (-12.3 to 12.2)
Age	Induprofen	Propranolol	-3.7 (-12.9 to 5.5)
Age	Induprofen	Rofecoxib	-4.0 (-16.2 to 8.3)
Age	Induprofen	Telmisartan	-4.1 (-16.3 to 8.2)
Age	Induprofen	Timolol	-7.3 (-19.5 to 5.0)
Age	Induprofen	Tizanidine	-4.6 (-16.8 to 7.7)
Age	Induprofen	Tolfenamic Acid	0.8 (-11.5 to 13.0)
Age	Induprofen	Tonabersat	-0.3 (-12.5 to 12.0)
Age	Induprofen	Topiramate	-5.6 (-14.7 to 3.6)
Age	Induprofen	Valproate	-4.3 (-14.9 to 6.4)
Age	Induprofen	Verapamil	-0.2 (-10.8 to 10.4)
Age	Induprofen	Vigabatrin	-7.9 (-20.1 to 4.4)
Age	Ketoprofen	Lamotrigine	-1.2 (-13.5 to 11.1)
Age	Ketoprofen	Lisinopril	-5.0 (-17.3 to 7.3)
Age	Ketoprofen	Magnesium	-6.4 (-17.0 to 4.2)
Age	Ketoprofen	Methysergide	-6.0 (-18.3 to 6.3)
Age	Ketoprofen	Metoprolol	-2.1 (-12.1 to 8.0)
Age	Ketoprofen	Montelukast	-4.0 (-16.3 to 8.3)
Age	Ketoprofen	Nadolol	-0.3 (-12.6 to 12.0)
Age	Ketoprofen	Naproxen sodium	-2.8 (-12.8 to 7.3)
Age	Ketoprofen	Nifedipine	6.2 (-6.1 to 18.5)
Age	Ketoprofen	Nimodipine	-0.7 (-10.7 to 9.4)
Age	Ketoprofen	Oxcarbazepine	-4.5 (-16.8 to 7.8)
Age	Ketoprofen	Pindolol	0.2 (-12.1 to 12.5)
Age	Ketoprofen	Propranolol	-3.5 (-12.7 to 5.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Ketoprofen	Rofecoxib	-3.7 (-16.0 to 8.6)
Age	Ketoprofen	Telmisartan	-3.8 (-16.1 to 8.5)
Age	Ketoprofen	Timolol	-7.0 (-19.3 to 5.3)
Age	Ketoprofen	Tizanidine	-4.3 (-16.6 to 8.0)
Age	Ketoprofen	Tolfenamic Acid	1.0 (-11.3 to 13.3)
Age	Ketoprofen	Tonabersat	0.0 (-12.3 to 12.3)
Age	Ketoprofen	Topiramate	-5.3 (-14.5 to 3.8)
Age	Ketoprofen	Valproate	-4.0 (-14.6 to 6.6)
Age	Ketoprofen	Verapamil	0.1 (-10.6 to 10.7)
Age	Ketoprofen	Vigabatrin	-7.6 (-19.9 to 4.7)
Age	Lamotrigine	Lisinopril	-3.8 (-16.1 to 8.5)
Age	Lamotrigine	Magnesium	-5.2 (-15.8 to 5.4)
Age	Lamotrigine	Methysergide	-4.8 (-17.1 to 7.5)
Age	Lamotrigine	Metoprolol	-0.9 (-10.9 to 9.2)
Age	Lamotrigine	Montelukast	-2.8 (-15.1 to 9.5)
Age	Lamotrigine	Nadolol	0.9 (-11.4 to 13.2)
Age	Lamotrigine	Naproxen sodium	-1.6 (-11.6 to 8.5)
Age	Lamotrigine	Nifedipine	7.4 (-4.9 to 19.7)
Age	Lamotrigine	Nimodipine	0.5 (-9.5 to 10.6)
Age	Lamotrigine	Oxcarbazepine	-3.3 (-15.6 to 9.0)
Age	Lamotrigine	Pindolol	1.4 (-10.9 to 13.7)
Age	Lamotrigine	Propranolol	-2.3 (-11.5 to 6.9)
Age	Lamotrigine	Rofecoxib	-2.5 (-14.8 to 9.8)
Age	Lamotrigine	Telmisartan	-2.6 (-14.9 to 9.7)
Age	Lamotrigine	Timolol	-5.8 (-18.1 to 6.5)
Age	Lamotrigine	Tizanidine	-3.1 (-15.4 to 9.2)
Age	Lamotrigine	Tolfenamic Acid	2.2 (-10.1 to 14.5)
Age	Lamotrigine	Tonabersat	1.2 (-11.1 to 13.5)
Age	Lamotrigine	Topiramate	-4.1 (-13.3 to 5.0)
Age	Lamotrigine	Valproate	-2.8 (-13.4 to 7.8)
Age	Lamotrigine	Verapamil	1.3 (-9.4 to 11.9)
Age	Lamotrigine	Vigabatrin	-6.4 (-18.7 to 5.9)
Age	Lisinopril	Magnesium	-1.4 (-12.0 to 9.2)
Age	Lisinopril	Methysergide	-1.0 (-13.3 to 11.3)
Age	Lisinopril	Metoprolol	2.9 (-7.1 to 13.0)
Age	Lisinopril	Montelukast	1.0 (-11.3 to 13.3)
Age	Lisinopril	Nadolol	4.7 (-7.6 to 17.0)
Age	Lisinopril	Naproxen sodium	2.2 (-7.8 to 12.3)
Age	Lisinopril	Nifedipine	11.2 (-1.1 to 23.5)
Age	Lisinopril	Nimodipine	4.3 (-5.7 to 14.4)
Age	Lisinopril	Oxcarbazepine	0.5 (-11.8 to 12.8)
Age	Lisinopril	Pindolol	5.2 (-7.1 to 17.5)
Age	Lisinopril	Propranolol	1.5 (-7.7 to 10.7)
Age	Lisinopril	Rofecoxib	1.3 (-11.0 to 13.6)
Age	Lisinopril	Telmisartan	1.2 (-11.1 to 13.5)
Age	Lisinopril	Timolol	-2.0 (-14.3 to 10.3)
Age	Lisinopril	Tizanidine	0.7 (-11.6 to 13.0)
Age	Lisinopril	Tolfenamic Acid	6.0 (-6.3 to 18.3)
Age	Lisinopril	Tonabersat	5.0 (-7.3 to 17.3)
Age	Lisinopril	Topiramate	-0.3 (-9.5 to 8.8)
Age	Lisinopril	Valproate	1.0 (-9.6 to 11.6)
Age	Lisinopril	Verapamil	5.1 (-5.6 to 15.7)
Age	Lisinopril	Vigabatrin	-2.6 (-14.9 to 9.7)
Age	Magnesium	Montelukast	2.4 (-8.2 to 13.0)
Age	Magnesium	Nadolol	6.1 (-4.5 to 16.7)
Age	Magnesium	Naproxen sodium	3.6 (-4.3 to 11.6)
Age	Magnesium	Nifedipine	12.6 (2.0 to 23.2)
Age	Magnesium	Nimodipine	5.7 (-2.2 to 13.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Magnesium	Oxcarbazepine	1.9 (-8.7 to 12.5)
Age	Magnesium	Pindolol	6.6 (-4.0 to 17.2)
Age	Magnesium	Propranolol	2.9 (-3.9 to 9.8)
Age	Magnesium	Rofecoxib	2.7 (-7.9 to 13.3)
Age	Magnesium	Telmisartan	2.6 (-8.0 to 13.2)
Age	Magnesium	Timolol	-0.6 (-11.2 to 10.0)
Age	Magnesium	Tizanidine	2.1 (-8.5 to 12.7)
Age	Magnesium	Tolfenamic Acid	7.4 (-3.2 to 18.0)
Age	Magnesium	Tonabersat	6.4 (-4.2 to 17.0)
Age	Magnesium	Topiramate	1.1 (-5.7 to 7.9)
Age	Magnesium	Valproate	2.4 (-6.3 to 11.1)
Age	Magnesium	Verapamil	6.5 (-2.2 to 15.1)
Age	Magnesium	Vigabatrin	-1.2 (-11.8 to 9.4)
Age	Methysergide	Magnesium	-0.4 (-11.0 to 10.2)
Age	Methysergide	Metoprolol	3.9 (-6.1 to 14.0)
Age	Methysergide	Montelukast	2.0 (-10.3 to 14.3)
Age	Methysergide	Nadolol	5.7 (-6.6 to 18.0)
Age	Methysergide	Naproxen sodium	3.2 (-6.8 to 13.3)
Age	Methysergide	Nifedipine	12.2 (-0.1 to 24.5)
Age	Methysergide	Nimodipine	5.3 (-4.7 to 15.4)
Age	Methysergide	Oxcarbazepine	1.5 (-10.8 to 13.8)
Age	Methysergide	Pindolol	6.2 (-6.1 to 18.5)
Age	Methysergide	Propranolol	2.5 (-6.7 to 11.7)
Age	Methysergide	Rofecoxib	2.3 (-10.0 to 14.6)
Age	Methysergide	Telmisartan	2.2 (-10.1 to 14.5)
Age	Methysergide	Timolol	-1.0 (-13.3 to 11.3)
Age	Methysergide	Tizanidine	1.7 (-10.6 to 14.0)
Age	Methysergide	Tolfenamic Acid	7.0 (-5.3 to 19.3)
Age	Methysergide	Tonabersat	6.0 (-6.3 to 18.3)
Age	Methysergide	Topiramate	0.7 (-8.5 to 9.8)
Age	Methysergide	Valproate	2.0 (-8.6 to 12.6)
Age	Methysergide	Verapamil	6.1 (-4.6 to 16.7)
Age	Methysergide	Vigabatrin	-1.6 (-13.9 to 10.7)
Age	Metoprolol	Magnesium	-4.3 (-12.3 to 3.6)
Age	Metoprolol	Montelukast	-1.9 (-12.0 to 8.1)
Age	Metoprolol	Nadolol	1.8 (-8.3 to 11.8)
Age	Metoprolol	Naproxen sodium	-0.7 (-7.8 to 6.4)
Age	Metoprolol	Nifedipine	8.3 (-1.8 to 18.3)
Age	Metoprolol	Nimodipine	1.4 (-5.7 to 8.5)
Age	Metoprolol	Oxcarbazepine	-2.4 (-12.5 to 7.6)
Age	Metoprolol	Pindolol	2.3 (-7.8 to 12.3)
Age	Metoprolol	Propranolol	-1.4 (-7.3 to 4.5)
Age	Metoprolol	Rofecoxib	-1.6 (-11.7 to 8.4)
Age	Metoprolol	Telmisartan	-1.7 (-11.8 to 8.3)
Age	Metoprolol	Timolol	-4.9 (-15.0 to 5.1)
Age	Metoprolol	Tizanidine	-2.2 (-12.3 to 7.8)
Age	Metoprolol	Tolfenamic Acid	3.1 (-7.0 to 13.1)
Age	Metoprolol	Tonabersat	2.1 (-8.0 to 12.1)
Age	Metoprolol	Topiramate	-3.3 (-9.0 to 2.5)
Age	Metoprolol	Valproate	-1.9 (-9.9 to 6.0)
Age	Metoprolol	Verapamil	2.1 (-5.8 to 10.0)
Age	Metoprolol	Vigabatrin	-5.5 (-15.6 to 4.5)
Age	Montelukast	Nadolol	3.7 (-8.6 to 16.0)
Age	Montelukast	Naproxen sodium	1.2 (-8.8 to 11.3)
Age	Montelukast	Nifedipine	10.2 (-2.1 to 22.5)
Age	Montelukast	Nimodipine	3.3 (-6.7 to 13.4)
Age	Montelukast	Oxcarbazepine	-0.5 (-12.8 to 11.8)
Age	Montelukast	Pindolol	4.2 (-8.1 to 16.5)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Montelukast	Propranolol	0.5 (-8.7 to 9.7)
Age	Montelukast	Rofecoxib	0.3 (-12.0 to 12.6)
Age	Montelukast	Telmisartan	0.2 (-12.1 to 12.5)
Age	Montelukast	Timolol	-3.0 (-15.3 to 9.3)
Age	Montelukast	Tizanidine	-0.3 (-12.6 to 12.0)
Age	Montelukast	Tolfenamic Acid	5.0 (-7.3 to 17.3)
Age	Montelukast	Tonabersat	4.0 (-8.3 to 16.3)
Age	Montelukast	Topiramate	-1.3 (-10.5 to 7.8)
Age	Montelukast	Valproate	0.0 (-10.6 to 10.6)
Age	Montelukast	Verapamil	4.1 (-6.6 to 14.7)
Age	Montelukast	Vigabatrin	-3.6 (-15.9 to 8.7)
Age	Nadolol	Naproxen sodium	-2.5 (-12.5 to 7.6)
Age	Nadolol	Nifedipine	6.5 (-5.8 to 18.8)
Age	Nadolol	Nimodipine	-0.4 (-10.4 to 9.7)
Age	Nadolol	Oxcarbazepine	-4.2 (-16.5 to 8.1)
Age	Nadolol	Pindolol	0.5 (-11.8 to 12.8)
Age	Nadolol	Propranolol	-3.2 (-12.4 to 6.0)
Age	Nadolol	Rofecoxib	-3.4 (-15.7 to 8.9)
Age	Nadolol	Telmisartan	-3.5 (-15.8 to 8.8)
Age	Nadolol	Timolol	-6.7 (-19.0 to 5.6)
Age	Nadolol	Tizanidine	-4.0 (-16.3 to 8.3)
Age	Nadolol	Tolfenamic Acid	1.3 (-11.0 to 13.6)
Age	Nadolol	Tonabersat	0.3 (-12.0 to 12.6)
Age	Nadolol	Topiramate	-5.0 (-14.2 to 4.1)
Age	Nadolol	Valproate	-3.7 (-14.3 to 6.9)
Age	Nadolol	Verapamil	0.4 (-10.3 to 11.0)
Age	Nadolol	Vigabatrin	-7.3 (-19.6 to 5.0)
Age	Naproxen sodium	Nifedipine	9.0 (-1.1 to 19.0)
Age	Naproxen sodium	Nimodipine	2.1 (-5.0 to 9.2)
Age	Naproxen sodium	Oxcarbazepine	-1.7 (-11.8 to 8.3)
Age	Naproxen sodium	Pindolol	3.0 (-7.1 to 13.0)
Age	Naproxen sodium	Propranolol	-0.7 (-6.6 to 5.2)
Age	Naproxen sodium	Rofecoxib	-0.9 (-11.0 to 9.1)
Age	Naproxen sodium	Telmisartan	-1.0 (-11.1 to 9.0)
Age	Naproxen sodium	Timolol	-4.2 (-14.3 to 5.8)
Age	Naproxen sodium	Tizanidine	-1.5 (-11.6 to 8.5)
Age	Naproxen sodium	Tolfenamic Acid	3.8 (-6.3 to 13.8)
Age	Naproxen sodium	Tonabersat	2.8 (-7.3 to 12.8)
Age	Naproxen sodium	Topiramate	-2.6 (-8.3 to 3.2)
Age	Naproxen sodium	Valproate	-1.2 (-9.2 to 6.7)
Age	Naproxen sodium	Verapamil	2.8 (-5.1 to 10.7)
Age	Naproxen sodium	Vigabatrin	-4.8 (-14.9 to 5.2)
Age	Nifedipine	Nimodipine	-6.9 (-16.9 to 3.2)
Age	Nifedipine	Oxcarbazepine	-10.7 (-23.0 to 1.6)
Age	Nifedipine	Pindolol	-6.0 (-18.3 to 6.3)
Age	Nifedipine	Propranolol	-9.7 (-18.9 to -0.5)
Age	Nifedipine	Rofecoxib	-9.9 (-22.2 to 2.4)
Age	Nifedipine	Telmisartan	-10.0 (-22.3 to 2.3)
Age	Nifedipine	Timolol	-13.2 (-25.5 to -0.9)
Age	Nifedipine	Tizanidine	-10.5 (-22.8 to 1.8)
Age	Nifedipine	Tolfenamic Acid	-5.2 (-17.5 to 7.1)
Age	Nifedipine	Tonabersat	-6.2 (-18.5 to 6.1)
Age	Nifedipine	Topiramate	-11.5 (-20.7 to -2.4)
Age	Nifedipine	Valproate	-10.2 (-20.8 to 0.4)
Age	Nifedipine	Verapamil	-6.2 (-16.8 to 4.5)
Age	Nifedipine	Vigabatrin	-13.8 (-26.1 to -1.5)
Age	Nimodipine	Oxcarbazepine	-3.8 (-13.9 to 6.2)
Age	Nimodipine	Pindolol	0.9 (-9.2 to 10.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Nimodipine	Propranolol	-2.8 (-8.7 to 3.1)
Age	Nimodipine	Rofecoxib	-3.0 (-13.1 to 7.0)
Age	Nimodipine	Telmisartan	-3.1 (-13.2 to 6.9)
Age	Nimodipine	Timolol	-6.3 (-16.4 to 3.7)
Age	Nimodipine	Tizanidine	-3.6 (-13.7 to 6.4)
Age	Nimodipine	Tolfenamic Acid	1.7 (-8.4 to 11.7)
Age	Nimodipine	Tonabersat	0.7 (-9.4 to 10.7)
Age	Nimodipine	Topiramate	-4.7 (-10.4 to 1.1)
Age	Nimodipine	Valproate	-3.3 (-11.3 to 4.6)
Age	Nimodipine	Verapamil	0.7 (-7.2 to 8.6)
Age	Nimodipine	Vigabatrin	-6.9 (-17.0 to 3.1)
Age	Oxcarbazepine	Pindolol	4.7 (-7.6 to 17.0)
Age	Oxcarbazepine	Propranolol	1.0 (-8.2 to 10.2)
Age	Oxcarbazepine	Rofecoxib	0.8 (-11.5 to 13.1)
Age	Oxcarbazepine	Telmisartan	0.7 (-11.6 to 13.0)
Age	Oxcarbazepine	Timolol	-2.5 (-14.8 to 9.8)
Age	Oxcarbazepine	Tizanidine	0.2 (-12.1 to 12.5)
Age	Oxcarbazepine	Tolfenamic Acid	5.5 (-6.8 to 17.8)
Age	Oxcarbazepine	Tonabersat	4.5 (-7.8 to 16.8)
Age	Oxcarbazepine	Topiramate	-0.8 (-10.0 to 8.3)
Age	Oxcarbazepine	Valproate	0.5 (-10.1 to 11.1)
Age	Oxcarbazepine	Verapamil	4.6 (-6.1 to 15.2)
Age	Oxcarbazepine	Vigabatrin	-3.1 (-15.4 to 9.2)
Age	Pindolol	Propranolol	-3.7 (-12.9 to 5.5)
Age	Pindolol	Rofecoxib	-3.9 (-16.2 to 8.4)
Age	Pindolol	Telmisartan	-4.0 (-16.3 to 8.3)
Age	Pindolol	Timolol	-7.2 (-19.5 to 5.1)
Age	Pindolol	Tizanidine	-4.5 (-16.8 to 7.8)
Age	Pindolol	Tolfenamic Acid	0.8 (-11.5 to 13.1)
Age	Pindolol	Tonabersat	-0.2 (-12.5 to 12.1)
Age	Pindolol	Topiramate	-5.5 (-14.7 to 3.6)
Age	Pindolol	Valproate	-4.2 (-14.8 to 6.4)
Age	Pindolol	Verapamil	-0.2 (-10.8 to 10.5)
Age	Pindolol	Vigabatrin	-7.8 (-20.1 to 4.5)
Age	Propranolol	Rofecoxib	-0.2 (-9.4 to 9.0)
Age	Propranolol	Telmisartan	-0.3 (-9.5 to 8.9)
Age	Propranolol	Timolol	-3.5 (-12.7 to 5.7)
Age	Propranolol	Tizanidine	-0.8 (-10.0 to 8.4)
Age	Propranolol	Tolfenamic Acid	4.5 (-4.7 to 13.7)
Age	Propranolol	Tonabersat	3.5 (-5.7 to 12.7)
Age	Propranolol	Topiramate	-1.8 (-6.1 to 2.4)
Age	Propranolol	Valproate	-0.5 (-7.4 to 6.3)
Age	Propranolol	Verapamil	3.5 (-3.3 to 10.4)
Age	Propranolol	Vigabatrin	-4.1 (-13.3 to 5.1)
Age	Rofecoxib	Telmisartan	-0.1 (-12.4 to 12.2)
Age	Rofecoxib	Timolol	-3.3 (-15.6 to 9.0)
Age	Rofecoxib	Tizanidine	-0.6 (-12.9 to 11.7)
Age	Rofecoxib	Tolfenamic Acid	4.7 (-7.6 to 17.0)
Age	Rofecoxib	Tonabersat	3.7 (-8.6 to 16.0)
Age	Rofecoxib	Topiramate	-1.6 (-10.8 to 7.5)
Age	Rofecoxib	Valproate	-0.3 (-10.9 to 10.3)
Age	Rofecoxib	Verapamil	3.8 (-6.9 to 14.4)
Age	Rofecoxib	Vigabatrin	-3.9 (-16.2 to 8.4)
Age	Telmisartan	Timolol	-3.2 (-15.5 to 9.1)
Age	Telmisartan	Tizanidine	-0.5 (-12.8 to 11.8)
Age	Telmisartan	Tolfenamic Acid	4.8 (-7.5 to 17.1)
Age	Telmisartan	Tonabersat	3.8 (-8.5 to 16.1)
Age	Telmisartan	Topiramate	-1.5 (-10.7 to 7.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Age	Telmisartan	Valproate	-0.2 (-10.8 to 10.4)
Age	Telmisartan	Verapamil	3.9 (-6.8 to 14.5)
Age	Telmisartan	Vigabatrin	-3.8 (-16.1 to 8.5)
Age	Timolol	Tizanidine	2.7 (-9.6 to 15.0)
Age	Timolol	Tolfenamic Acid	8.0 (-4.3 to 20.3)
Age	Timolol	Tonabersat	7.0 (-5.3 to 19.3)
Age	Timolol	Topiramate	1.7 (-7.5 to 10.8)
Age	Timolol	Valproate	3.0 (-7.6 to 13.6)
Age	Timolol	Verapamil	7.1 (-3.6 to 17.7)
Age	Timolol	Vigabatrin	-0.6 (-12.9 to 11.7)
Age	Tizanidine	Tolfenamic Acid	5.3 (-7.0 to 17.6)
Age	Tizanidine	Tonabersat	4.3 (-8.0 to 16.6)
Age	Tizanidine	Topiramate	-1.0 (-10.2 to 8.1)
Age	Tizanidine	Valproate	0.3 (-10.3 to 10.9)
Age	Tizanidine	Verapamil	4.4 (-6.3 to 15.0)
Age	Tizanidine	Vigabatrin	-3.3 (-15.6 to 9.0)
Age	Tolfenamic Acid	Tonabersat	-1.0 (-13.3 to 11.3)
Age	Tolfenamic Acid	Topiramate	-6.3 (-15.5 to 2.8)
Age	Tolfenamic Acid	Valproate	-5.0 (-15.6 to 5.6)
Age	Tolfenamic Acid	Verapamil	-1.0 (-11.6 to 9.7)
Age	Tolfenamic Acid	Vigabatrin	-8.6 (-20.9 to 3.7)
Age	Tonabersat	Topiramate	-5.3 (-14.5 to 3.8)
Age	Tonabersat	Valproate	-4.0 (-14.6 to 6.6)
Age	Tonabersat	Verapamil	0.1 (-10.6 to 10.7)
Age	Tonabersat	Vigabatrin	-7.6 (-19.9 to 4.7)
Age	Topiramate	Valproate	1.3 (-5.5 to 8.1)
Age	Topiramate	Verapamil	5.4 (-1.4 to 12.2)
Age	Topiramate	Vigabatrin	-2.3 (-11.4 to 6.9)
Age	Valproate	Verapamil	4.1 (-4.6 to 12.7)
Age	Valproate	Vigabatrin	-3.6 (-14.2 to 7.0)
Age	Verapamil	Vigabatrin	-7.7 (-18.3 to 3.0)
% females	Acebutolol	Acetazolamide	-1.1 (-45.6 to 43.4)
% females	Acebutolol	Alprenolol	-7.4 (-51.9 to 37.1)
% females	Acebutolol	Amitriptyline	-8.9 (-45.2 to 27.4)
% females	Acebutolol	Aspirin	12.9 (-25.4 to 51.2)
% females	Acebutolol	Atenolol	-0.5 (-39.0 to 38.0)
% females	Acebutolol	Candesartan	-4.6 (-49.1 to 39.9)
% females	Acebutolol	Captopril	16.4 (-28.1 to 60.9)
% females	Acebutolol	Carbamazepine	5.6 (-38.9 to 50.1)
% females	Acebutolol	Clonidine	-3.1 (-35.8 to 29.6)
% females	Acebutolol	Dihydroergocryptine	2.8 (-41.7 to 47.3)
% females	Acebutolol	Dihydroergotamine	4.2 (-32.1 to 40.5)
% females	Acebutolol	Divalproex	-3.9 (-42.4 to 34.6)
% females	Acebutolol	Femoxetine	-7.8 (-44.1 to 28.5)
% females	Acebutolol	Fluoxetine	-3.0 (-38.2 to 32.1)
% females	Acebutolol	Gabapentin	-0.3 (-36.6 to 36.0)
% females	Acebutolol	Guanfacine	-9.6 (-54.1 to 34.9)
% females	Acebutolol	Indobufen	6.4 (-38.1 to 50.9)
% females	Acebutolol	Indomethacin	-1.6 (-46.1 to 42.9)
% females	Acebutolol	Induprofen	14.4 (-30.1 to 58.9)
% females	Acebutolol	Ketoprofen	-13.6 (-58.1 to 30.9)
% females	Acebutolol	Lamotrigine	-7.4 (-51.9 to 37.1)
% females	Acebutolol	Lisinopril	-6.6 (-51.1 to 37.9)
% females	Acebutolol	Methysergide	-5.6 (-50.1 to 38.9)
% females	Acebutolol	Metoprolol	-8.7 (-45.0 to 27.6)
% females	Acebutolol	Magnesium	-15.1 (-53.6 to 23.4)
% females	Acebutolol	Montelukast	-13.6 (-58.1 to 30.9)
% females	Acebutolol	Nadolol	-6.9 (-51.4 to 37.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Acebutolol	Naproxen sodium	-4.9 (-41.2 to 31.4)
% females	Acebutolol	Nicardipine	1.4 (-43.1 to 45.9)
% females	Acebutolol	Nifedipine	-4.6 (-49.1 to 39.9)
% females	Acebutolol	Nimodipine	4.1 (-32.2 to 40.4)
% females	Acebutolol	Oxcarbazepine	-10.3 (-54.8 to 34.2)
% females	Acebutolol	Pindolol	-11.3 (-55.8 to 33.2)
% females	Acebutolol	Propranolol	-3.7 (-36.7 to 29.3)
% females	Acebutolol	Rofecoxib	-10.1 (-54.6 to 34.4)
% females	Acebutolol	Telmisartan	-10.1 (-54.6 to 34.4)
% females	Acebutolol	Timolol	2.7 (-35.8 to 41.2)
% females	Acebutolol	Tizanidine	-4.6 (-49.1 to 39.9)
% females	Acebutolol	Tolfenamic Acid	-12.6 (-57.1 to 31.9)
% females	Acebutolol	Tonabersat	-17.9 (-62.4 to 26.6)
% females	Acebutolol	Topiramate	4.4 (-28.8 to 37.5)
% females	Acebutolol	Valproate	-8.3 (-46.8 to 30.3)
% females	Acebutolol	Verapamil	-6.1 (-44.6 to 32.4)
% females	Acebutolol	Vigabatrin	0.5 (-44.0 to 45.0)
% females	Acetazolamide	Alprenolol	-6.3 (-50.8 to 38.2)
% females	Acetazolamide	Amitriptyline	-7.8 (-44.1 to 28.5)
% females	Acetazolamide	Aspirin	14.0 (-24.3 to 52.3)
% females	Acetazolamide	Atenolol	0.6 (-37.9 to 39.1)
% females	Acetazolamide	Candesartan	-3.5 (-48.0 to 41.0)
% females	Acetazolamide	Captopril	17.5 (-27.0 to 62.0)
% females	Acetazolamide	Carbamazepine	6.7 (-37.8 to 51.2)
% females	Acetazolamide	Clonidine	-2.0 (-34.7 to 30.7)
% females	Acetazolamide	Dihydroergocryptine	3.9 (-40.6 to 48.4)
% females	Acetazolamide	Dihydroergotamine	5.3 (-31.0 to 41.6)
% females	Acetazolamide	Divalproex	-2.8 (-41.3 to 35.7)
% females	Acetazolamide	Femoxetine	-6.7 (-43.0 to 29.6)
% females	Acetazolamide	Fluoxetine	-1.9 (-37.1 to 33.2)
% females	Acetazolamide	Gabapentin	0.8 (-35.5 to 37.1)
% females	Acetazolamide	Guanfacine	-8.5 (-53.0 to 36.0)
% females	Acetazolamide	Indobufen	7.5 (-37.0 to 52.0)
% females	Acetazolamide	Indomethacin	-0.5 (-45.0 to 44.0)
% females	Acetazolamide	Induprofen	15.5 (-29.0 to 60.0)
% females	Acetazolamide	Ketoprofen	-12.5 (-57.0 to 32.0)
% females	Acetazolamide	Lamotrigine	-6.3 (-50.8 to 38.2)
% females	Acetazolamide	Lisinopril	-5.5 (-50.0 to 39.0)
% females	Acetazolamide	Methysergide	-4.5 (-49.0 to 40.0)
% females	Acetazolamide	Metoprolol	-7.6 (-43.9 to 28.7)
% females	Acetazolamide	Magnesium	-14.0 (-52.5 to 24.5)
% females	Acetazolamide	Montelukast	-12.5 (-57.0 to 32.0)
% females	Acetazolamide	Nadolol	-5.8 (-50.3 to 38.7)
% females	Acetazolamide	Naproxen sodium	-3.8 (-40.1 to 32.5)
% females	Acetazolamide	Nicardipine	2.5 (-42.0 to 47.0)
% females	Acetazolamide	Nifedipine	-3.5 (-48.0 to 41.0)
% females	Acetazolamide	Nimodipine	5.2 (-31.1 to 41.5)
% females	Acetazolamide	Oxcarbazepine	-9.2 (-53.7 to 35.3)
% females	Acetazolamide	Pindolol	-10.2 (-54.7 to 34.3)
% females	Acetazolamide	Propranolol	-2.6 (-35.6 to 30.4)
% females	Acetazolamide	Rofecoxib	-9.0 (-53.5 to 35.5)
% females	Acetazolamide	Telmisartan	-9.0 (-53.5 to 35.5)
% females	Acetazolamide	Timolol	3.8 (-34.7 to 42.3)
% females	Acetazolamide	Tizanidine	-3.5 (-48.0 to 41.0)
% females	Acetazolamide	Tolfenamic Acid	-11.5 (-56.0 to 33.0)
% females	Acetazolamide	Tonabersat	-16.8 (-61.3 to 27.7)
% females	Acetazolamide	Topiramate	5.5 (-27.7 to 38.6)
% females	Acetazolamide	Valproate	-7.2 (-45.7 to 31.4)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Acetazolamide	Verapamil	-5.0 (-43.5 to 33.5)
% females	Acetazolamide	Vigabatrin	1.6 (-42.9 to 46.1)
% females	Alprenolol	Amitriptyline	-1.5 (-37.8 to 34.8)
% females	Alprenolol	Aspirin	20.3 (-18.0 to 58.6)
% females	Alprenolol	Atenolol	6.9 (-31.6 to 45.4)
% females	Alprenolol	Candesartan	2.8 (-41.7 to 47.3)
% females	Alprenolol	Captopril	23.8 (-20.7 to 68.3)
% females	Alprenolol	Carbamazepine	13.0 (-31.5 to 57.5)
% females	Alprenolol	Clonidine	4.3 (-28.4 to 37.0)
% females	Alprenolol	Dihydroergocryptine	10.2 (-34.3 to 54.7)
% females	Alprenolol	Dihydroergotamine	11.6 (-24.7 to 47.9)
% females	Alprenolol	Divalproex	3.5 (-35.0 to 42.0)
% females	Alprenolol	Femoxetine	-0.4 (-36.7 to 35.9)
% females	Alprenolol	Fluoxetine	4.4 (-30.8 to 39.5)
% females	Alprenolol	Gabapentin	7.1 (-29.2 to 43.4)
% females	Alprenolol	Guanfacine	-2.2 (-46.7 to 42.3)
% females	Alprenolol	Indobufen	13.8 (-30.7 to 58.3)
% females	Alprenolol	Indomethacin	5.8 (-38.7 to 50.3)
% females	Alprenolol	Induprofen	21.8 (-22.7 to 66.3)
% females	Alprenolol	Ketoprofen	-6.2 (-50.7 to 38.3)
% females	Alprenolol	Lamotrigine	0.0 (-44.5 to 44.5)
% females	Alprenolol	Lisinopril	0.8 (-43.7 to 45.3)
% females	Alprenolol	Methysergide	1.8 (-42.7 to 46.3)
% females	Alprenolol	Metoprolol	-1.3 (-37.6 to 35.0)
% females	Alprenolol	Magnesium	-7.7 (-46.2 to 30.8)
% females	Alprenolol	Montelukast	-6.2 (-50.7 to 38.3)
% females	Alprenolol	Nadolol	0.5 (-44.0 to 45.0)
% females	Alprenolol	Naproxen sodium	2.5 (-33.8 to 38.8)
% females	Alprenolol	Nicardipine	8.8 (-35.7 to 53.3)
% females	Alprenolol	Nifedipine	2.8 (-41.7 to 47.3)
% females	Alprenolol	Nimodipine	11.5 (-24.8 to 47.8)
% females	Alprenolol	Oxcarbazepine	-2.9 (-47.4 to 41.6)
% females	Alprenolol	Pindolol	-3.9 (-48.4 to 40.6)
% females	Alprenolol	Propranolol	3.7 (-29.3 to 36.7)
% females	Alprenolol	Rofecoxib	-2.7 (-47.2 to 41.8)
% females	Alprenolol	Telmisartan	-2.7 (-47.2 to 41.8)
% females	Alprenolol	Timolol	10.1 (-28.4 to 48.6)
% females	Alprenolol	Tizanidine	2.8 (-41.7 to 47.3)
% females	Alprenolol	Tolfenamic Acid	-5.2 (-49.7 to 39.3)
% females	Alprenolol	Tonabersat	-10.5 (-55.0 to 34.0)
% females	Alprenolol	Topiramate	11.8 (-21.4 to 44.9)
% females	Alprenolol	Valproate	-0.9 (-39.4 to 37.7)
% females	Alprenolol	Verapamil	1.3 (-37.2 to 39.8)
% females	Alprenolol	Vigabatrin	7.9 (-36.6 to 52.4)
% females	Amitriptyline	Aspirin	21.8 (-4.3 to 47.9)
% females	Amitriptyline	Atenolol	8.4 (-20.3 to 37.1)
% females	Amitriptyline	Candesartan	4.3 (-32.0 to 40.6)
% females	Amitriptyline	Captopril	25.3 (-11.0 to 61.6)
% females	Amitriptyline	Carbamazepine	14.5 (-21.8 to 50.8)
% females	Amitriptyline	Clonidine	5.8 (-14.5 to 26.1)
% females	Amitriptyline	Dihydroergocryptine	11.7 (-24.6 to 48.0)
% females	Amitriptyline	Dihydroergotamine	13.1 (-12.6 to 38.7)
% females	Amitriptyline	Divalproex	5.0 (-23.7 to 33.7)
% females	Amitriptyline	Femoxetine	1.1 (-24.6 to 26.8)
% females	Amitriptyline	Fluoxetine	5.9 (-18.1 to 29.9)
% females	Amitriptyline	Gabapentin	8.6 (-17.1 to 34.3)
% females	Amitriptyline	Guanfacine	-0.7 (-37.0 to 35.6)
% females	Amitriptyline	Indobufen	15.3 (-21.0 to 51.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Amitriptyline	Indomethacin	7.3 (-29.0 to 43.6)
% females	Amitriptyline	Induprofen	23.3 (-13.0 to 59.6)
% females	Amitriptyline	Ketoprofen	-4.7 (-41.0 to 31.6)
% females	Amitriptyline	Lamotrigine	1.5 (-34.8 to 37.8)
% females	Amitriptyline	Lisinopril	2.3 (-34.0 to 38.6)
% females	Amitriptyline	Methysergide	3.3 (-33.0 to 39.6)
% females	Amitriptyline	Metoprolol	0.2 (-25.4 to 25.9)
% females	Amitriptyline	Magnesium	-6.2 (-34.9 to 22.5)
% females	Amitriptyline	Montelukast	-4.7 (-41.0 to 31.6)
% females	Amitriptyline	Nadolol	2.0 (-34.3 to 38.3)
% females	Amitriptyline	Naproxen sodium	4.0 (-21.7 to 29.6)
% females	Amitriptyline	Nicardipine	10.3 (-26.0 to 46.6)
% females	Amitriptyline	Nifedipine	4.3 (-32.0 to 40.6)
% females	Amitriptyline	Nimodipine	13.0 (-12.7 to 38.6)
% females	Amitriptyline	Oxcarbazepine	-1.4 (-37.7 to 34.9)
% females	Amitriptyline	Pindolol	-2.4 (-38.7 to 33.9)
% females	Amitriptyline	Propranolol	5.2 (-15.5 to 25.9)
% females	Amitriptyline	Rofecoxib	-1.2 (-37.5 to 35.1)
% females	Amitriptyline	Telmisartan	-1.2 (-37.5 to 35.1)
% females	Amitriptyline	Timolol	11.6 (-17.1 to 40.3)
% females	Amitriptyline	Tizanidine	4.3 (-32.0 to 40.6)
% females	Amitriptyline	Tolfenamic Acid	-3.7 (-40.0 to 32.6)
% females	Amitriptyline	Tonabersat	-9.0 (-45.3 to 27.3)
% females	Amitriptyline	Topiramate	13.3 (-7.7 to 34.3)
% females	Amitriptyline	Valproate	0.7 (-28.1 to 29.4)
% females	Amitriptyline	Verapamil	2.8 (-25.9 to 31.5)
% females	Amitriptyline	Vigabatrin	9.4 (-26.9 to 45.7)
% females	Aspirin	Atenolol	-13.4 (-43.0 to 16.2)
% females	Aspirin	Candesartan	-17.5 (-55.8 to 20.8)
% females	Aspirin	Captopril	3.5 (-34.8 to 41.8)
% females	Aspirin	Carbamazepine	-7.3 (-45.6 to 31.0)
% females	Aspirin	Clonidine	-16.0 (-35.8 to 3.8)
% females	Aspirin	Dihydroergocryptine	-10.1 (-48.4 to 28.2)
% females	Aspirin	Dihydroergotamine	-8.7 (-34.9 to 17.4)
% females	Aspirin	Divalproex	-16.8 (-46.4 to 12.8)
% females	Aspirin	Femoxetine	-20.7 (-46.8 to 5.4)
% females	Aspirin	Fluoxetine	-15.9 (-40.1 to 8.3)
% females	Aspirin	Gabapentin	-13.2 (-39.3 to 12.9)
% females	Aspirin	Guanfacine	-22.5 (-60.8 to 15.8)
% females	Aspirin	Indobufen	-6.5 (-44.8 to 31.8)
% females	Aspirin	Indomethacin	-14.5 (-52.8 to 23.8)
% females	Aspirin	Induprofen	1.5 (-36.8 to 39.8)
% females	Aspirin	Ketoprofen	-26.5 (-64.8 to 11.8)
% females	Aspirin	Lamotrigine	-20.3 (-58.6 to 18.0)
% females	Aspirin	Lisinopril	-19.5 (-57.8 to 18.8)
% females	Aspirin	Methysergide	-18.5 (-56.8 to 19.8)
% females	Aspirin	Metoprolol	-21.6 (-47.7 to 4.6)
% females	Aspirin	Magnesium	-28.0 (-57.6 to 1.6)
% females	Aspirin	Montelukast	-26.5 (-64.8 to 11.8)
% females	Aspirin	Nadolol	-19.8 (-58.1 to 18.5)
% females	Aspirin	Naproxen sodium	-17.8 (-44.0 to 8.3)
% females	Aspirin	Nicardipine	-11.5 (-49.8 to 26.8)
% females	Aspirin	Nifedipine	-17.5 (-55.8 to 20.8)
% females	Aspirin	Nimodipine	-8.8 (-35.0 to 17.3)
% females	Aspirin	Oxcarbazepine	-23.2 (-61.5 to 15.1)
% females	Aspirin	Pindolol	-24.2 (-62.5 to 14.1)
% females	Aspirin	Propranolol	-16.6 (-36.9 to 3.6)
% females	Aspirin	Rofecoxib	-23.0 (-61.3 to 15.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Aspirin	Telmisartan	-23.0 (-61.3 to 15.3)
% females	Aspirin	Timolol	-10.2 (-39.8 to 19.4)
% females	Aspirin	Tizanidine	-17.5 (-55.8 to 20.8)
% females	Aspirin	Tolfenamic Acid	-25.5 (-63.8 to 12.8)
% females	Aspirin	Tonabersat	-30.8 (-69.1 to 7.5)
% females	Aspirin	Topiramate	-8.5 (-29.1 to 12.0)
% females	Aspirin	Valproate	-21.2 (-50.8 to 8.5)
% females	Aspirin	Verapamil	-19.0 (-48.6 to 10.6)
% females	Aspirin	Vigabatrin	-12.4 (-50.7 to 25.9)
% females	Atenolol	Candesartan	-4.1 (-42.6 to 34.4)
% females	Atenolol	Captopril	16.9 (-21.6 to 55.4)
% females	Atenolol	Carbamazepine	6.1 (-32.4 to 44.6)
% females	Atenolol	Clonidine	-2.6 (-26.6 to 21.4)
% females	Atenolol	Dihydroergocryptine	3.3 (-35.2 to 41.8)
% females	Atenolol	Dihydroergotamine	4.7 (-24.0 to 33.4)
% females	Atenolol	Divalproex	-3.4 (-34.8 to 28.0)
% females	Atenolol	Femoxetine	-7.3 (-36.0 to 21.4)
% females	Atenolol	Fluoxetine	-2.5 (-29.8 to 24.7)
% females	Atenolol	Gabapentin	0.2 (-28.5 to 28.9)
% females	Atenolol	Guanfacine	-9.1 (-47.6 to 29.4)
% females	Atenolol	Indobufen	6.9 (-31.6 to 45.4)
% females	Atenolol	Indomethacin	-1.1 (-39.6 to 37.4)
% females	Atenolol	Induprofen	14.9 (-23.6 to 53.4)
% females	Atenolol	Ketoprofen	-13.1 (-51.6 to 25.4)
% females	Atenolol	Lamotrigine	-6.9 (-45.4 to 31.6)
% females	Atenolol	Lisinopril	-6.1 (-44.6 to 32.4)
% females	Atenolol	Methysergide	-5.1 (-43.6 to 33.4)
% females	Atenolol	Metoprolol	-8.2 (-36.9 to 20.5)
% females	Atenolol	Magnesium	-14.6 (-46.0 to 16.8)
% females	Atenolol	Montelukast	-13.1 (-51.6 to 25.4)
% females	Atenolol	Nadolol	-6.4 (-44.9 to 32.1)
% females	Atenolol	Naproxen sodium	-4.4 (-33.1 to 24.3)
% females	Atenolol	Nicardipine	1.9 (-36.6 to 40.4)
% females	Atenolol	Nifedipine	-4.1 (-42.6 to 34.4)
% females	Atenolol	Nimodipine	4.6 (-24.1 to 33.3)
% females	Atenolol	Oxcarbazepine	-9.8 (-48.3 to 28.7)
% females	Atenolol	Pindolol	-10.8 (-49.3 to 27.7)
% females	Atenolol	Propranolol	-3.2 (-27.6 to 21.2)
% females	Atenolol	Rofecoxib	-9.6 (-48.1 to 28.9)
% females	Atenolol	Telmisartan	-9.6 (-48.1 to 28.9)
% females	Atenolol	Timolol	3.2 (-28.2 to 34.6)
% females	Atenolol	Tizanidine	-4.1 (-42.6 to 34.4)
% females	Atenolol	Tolfenamic Acid	-12.1 (-50.6 to 26.4)
% females	Atenolol	Tonabersat	-17.4 (-55.9 to 21.1)
% females	Atenolol	Topiramate	4.9 (-19.7 to 29.5)
% females	Atenolol	Valproate	-7.8 (-39.2 to 23.7)
% females	Atenolol	Verapamil	-5.6 (-37.0 to 25.8)
% females	Atenolol	Vigabatrin	1.0 (-37.5 to 39.5)
% females	Candesartan	Captopril	21.0 (-23.5 to 65.5)
% females	Candesartan	Carbamazepine	10.2 (-34.3 to 54.7)
% females	Candesartan	Clonidine	1.5 (-31.2 to 34.2)
% females	Candesartan	Dihydroergocryptine	7.4 (-37.1 to 51.9)
% females	Candesartan	Dihydroergotamine	8.8 (-27.5 to 45.1)
% females	Candesartan	Divalproex	0.7 (-37.8 to 39.2)
% females	Candesartan	Femoxetine	-3.2 (-39.5 to 33.1)
% females	Candesartan	Fluoxetine	1.6 (-33.6 to 36.7)
% females	Candesartan	Gabapentin	4.3 (-32.0 to 40.6)
% females	Candesartan	Guanfacine	-5.0 (-49.5 to 39.5)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Candesartan	Indobufen	11.0 (-33.5 to 55.5)
% females	Candesartan	Indomethacin	3.0 (-41.5 to 47.5)
% females	Candesartan	Induprofen	19.0 (-25.5 to 63.5)
% females	Candesartan	Ketoprofen	-9.0 (-53.5 to 35.5)
% females	Candesartan	Lamotrigine	-2.8 (-47.3 to 41.7)
% females	Candesartan	Lisinopril	-2.0 (-46.5 to 42.5)
% females	Candesartan	Methysergide	-1.0 (-45.5 to 43.5)
% females	Candesartan	Metoprolol	-4.1 (-40.4 to 32.2)
% females	Candesartan	Magnesium	-10.5 (-49.0 to 28.0)
% females	Candesartan	Montelukast	-9.0 (-53.5 to 35.5)
% females	Candesartan	Nadolol	-2.3 (-46.8 to 42.2)
% females	Candesartan	Naproxen sodium	-0.3 (-36.6 to 36.0)
% females	Candesartan	Nicardipine	6.0 (-38.5 to 50.5)
% females	Candesartan	Nifedipine	0.0 (-44.5 to 44.5)
% females	Candesartan	Nimodipine	8.7 (-27.6 to 45.0)
% females	Candesartan	Oxcarbazepine	-5.7 (-50.2 to 38.8)
% females	Candesartan	Pindolol	-6.7 (-51.2 to 37.8)
% females	Candesartan	Propranolol	0.9 (-32.1 to 33.9)
% females	Candesartan	Rofecoxib	-5.5 (-50.0 to 39.0)
% females	Candesartan	Telmisartan	-5.5 (-50.0 to 39.0)
% females	Candesartan	Timolol	7.3 (-31.2 to 45.8)
% females	Candesartan	Tizanidine	0.0 (-44.5 to 44.5)
% females	Candesartan	Tolfenamic Acid	-8.0 (-52.5 to 36.5)
% females	Candesartan	Tonabersat	-13.3 (-57.8 to 31.2)
% females	Candesartan	Topiramate	9.0 (-24.2 to 42.1)
% females	Candesartan	Valproate	-3.7 (-42.2 to 34.9)
% females	Candesartan	Verapamil	-1.5 (-40.0 to 37.0)
% females	Candesartan	Vigabatrin	5.1 (-39.4 to 49.6)
% females	Captopril	Carbamazepine	-10.8 (-55.3 to 33.7)
% females	Captopril	Clonidine	-19.5 (-52.2 to 13.2)
% females	Captopril	Dihydroergocryptine	-13.6 (-58.1 to 30.9)
% females	Captopril	Dihydroergotamine	-12.2 (-48.5 to 24.1)
% females	Captopril	Divalproex	-20.3 (-58.8 to 18.2)
% females	Captopril	Femoxetine	-24.2 (-60.5 to 12.1)
% females	Captopril	Fluoxetine	-19.4 (-54.6 to 15.7)
% females	Captopril	Gabapentin	-16.7 (-53.0 to 19.6)
% females	Captopril	Guanfacine	-26.0 (-70.5 to 18.5)
% females	Captopril	Indobufen	-10.0 (-54.5 to 34.5)
% females	Captopril	Indomethacin	-18.0 (-62.5 to 26.5)
% females	Captopril	Induprofen	-2.0 (-46.5 to 42.5)
% females	Captopril	Ketoprofen	-30.0 (-74.5 to 14.5)
% females	Captopril	Lamotrigine	-23.8 (-68.3 to 20.7)
% females	Captopril	Lisinopril	-23.0 (-67.5 to 21.5)
% females	Captopril	Methysergide	-22.0 (-66.5 to 22.5)
% females	Captopril	Metoprolol	-25.1 (-61.4 to 11.2)
% females	Captopril	Magnesium	-31.5 (-70.0 to 7.0)
% females	Captopril	Montelukast	-30.0 (-74.5 to 14.5)
% females	Captopril	Nadolol	-23.3 (-67.8 to 21.2)
% females	Captopril	Naproxen sodium	-21.3 (-57.6 to 15.0)
% females	Captopril	Nicardipine	-15.0 (-59.5 to 29.5)
% females	Captopril	Nifedipine	-21.0 (-65.5 to 23.5)
% females	Captopril	Nimodipine	-12.3 (-48.6 to 24.0)
% females	Captopril	Oxcarbazepine	-26.7 (-71.2 to 17.8)
% females	Captopril	Pindolol	-27.7 (-72.2 to 16.8)
% females	Captopril	Propranolol	-20.1 (-53.1 to 12.9)
% females	Captopril	Rofecoxib	-26.5 (-71.0 to 18.0)
% females	Captopril	Telmisartan	-26.5 (-71.0 to 18.0)
% females	Captopril	Timolol	-13.7 (-52.2 to 24.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Captopril	Tizanidine	-21.0 (-65.5 to 23.5)
% females	Captopril	Tolfenamic Acid	-29.0 (-73.5 to 15.5)
% females	Captopril	Tonabersat	-34.3 (-78.8 to 10.2)
% females	Captopril	Topiramate	-12.0 (-45.2 to 21.1)
% females	Captopril	Valproate	-24.7 (-63.2 to 13.9)
% females	Captopril	Verapamil	-22.5 (-61.0 to 16.0)
% females	Captopril	Vigabatrin	-15.9 (-60.4 to 28.6)
% females	Carbamazepine	Clonidine	-8.7 (-41.4 to 24.0)
% females	Carbamazepine	Dihydroergocryptine	-2.8 (-47.3 to 41.7)
% females	Carbamazepine	Dihydroergotamine	-1.4 (-37.7 to 34.9)
% females	Carbamazepine	Divalproex	-9.5 (-48.0 to 29.0)
% females	Carbamazepine	Femoxetine	-13.4 (-49.7 to 22.9)
% females	Carbamazepine	Fluoxetine	-8.6 (-43.8 to 26.5)
% females	Carbamazepine	Gabapentin	-5.9 (-42.2 to 30.4)
% females	Carbamazepine	Guanfacine	-15.2 (-59.7 to 29.3)
% females	Carbamazepine	Indobufen	0.8 (-43.7 to 45.3)
% females	Carbamazepine	Indomethacin	-7.2 (-51.7 to 37.3)
% females	Carbamazepine	Induprofen	8.8 (-35.7 to 53.3)
% females	Carbamazepine	Ketoprofen	-19.2 (-63.7 to 25.3)
% females	Carbamazepine	Lamotrigine	-13.0 (-57.5 to 31.5)
% females	Carbamazepine	Lisinopril	-12.2 (-56.7 to 32.3)
% females	Carbamazepine	Methysergide	-11.2 (-55.7 to 33.3)
% females	Carbamazepine	Metoprolol	-14.3 (-50.6 to 22.0)
% females	Carbamazepine	Magnesium	-20.7 (-59.2 to 17.8)
% females	Carbamazepine	Montelukast	-19.2 (-63.7 to 25.3)
% females	Carbamazepine	Nadolol	-12.5 (-57.0 to 32.0)
% females	Carbamazepine	Naproxen sodium	-10.5 (-46.8 to 25.8)
% females	Carbamazepine	Nicardipine	-4.2 (-48.7 to 40.3)
% females	Carbamazepine	Nifedipine	-10.2 (-54.7 to 34.3)
% females	Carbamazepine	Nimodipine	-1.5 (-37.8 to 34.8)
% females	Carbamazepine	Oxcarbazepine	-15.9 (-60.4 to 28.6)
% females	Carbamazepine	Pindolol	-16.9 (-61.4 to 27.6)
% females	Carbamazepine	Propranolol	-9.3 (-42.3 to 23.7)
% females	Carbamazepine	Rofecoxib	-15.7 (-60.2 to 28.8)
% females	Carbamazepine	Telmisartan	-15.7 (-60.2 to 28.8)
% females	Carbamazepine	Timolol	-2.9 (-41.4 to 35.6)
% females	Carbamazepine	Tizanidine	-10.2 (-54.7 to 34.3)
% females	Carbamazepine	Tolfenamic Acid	-18.2 (-62.7 to 26.3)
% females	Carbamazepine	Tonabersat	-23.5 (-68.0 to 21.0)
% females	Carbamazepine	Topiramate	-1.2 (-34.4 to 31.9)
% females	Carbamazepine	Valproate	-13.9 (-52.4 to 24.7)
% females	Carbamazepine	Verapamil	-11.7 (-50.2 to 26.8)
% females	Carbamazepine	Vigabatrin	-5.1 (-49.6 to 39.4)
% females	Clonidine	Dihydroergocryptine	5.9 (-26.8 to 38.6)
% females	Clonidine	Dihydroergotamine	7.3 (-13.0 to 27.6)
% females	Clonidine	Divalproex	-0.8 (-24.8 to 23.2)
% females	Clonidine	Femoxetine	-4.7 (-25.0 to 15.6)
% females	Clonidine	Fluoxetine	0.1 (-18.1 to 18.2)
% females	Clonidine	Gabapentin	2.8 (-17.5 to 23.1)
% females	Clonidine	Guanfacine	-6.5 (-39.2 to 26.2)
% females	Clonidine	Indobufen	9.5 (-23.2 to 42.2)
% females	Clonidine	Indomethacin	1.5 (-31.2 to 34.2)
% females	Clonidine	Induprofen	17.5 (-15.2 to 50.2)
% females	Clonidine	Ketoprofen	-10.5 (-43.2 to 22.2)
% females	Clonidine	Lamotrigine	-4.3 (-37.0 to 28.4)
% females	Clonidine	Lisinopril	-3.5 (-36.2 to 29.2)
% females	Clonidine	Methysergide	-2.5 (-35.2 to 30.2)
% females	Clonidine	Metoprolol	-5.6 (-25.9 to 14.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Clonidine	Magnesium	-12.0 (-36.0 to 12.0)
% females	Clonidine	Montelukast	-10.5 (-43.2 to 22.2)
% females	Clonidine	Nadolol	-3.8 (-36.5 to 28.9)
% females	Clonidine	Naproxen sodium	-1.8 (-22.1 to 18.5)
% females	Clonidine	Nicardipine	4.5 (-28.2 to 37.2)
% females	Clonidine	Nifedipine	-1.5 (-34.2 to 31.2)
% females	Clonidine	Nimodipine	7.2 (-13.1 to 27.5)
% females	Clonidine	Oxcarbazepine	-7.2 (-39.9 to 25.5)
% females	Clonidine	Pindolol	-8.2 (-40.9 to 24.5)
% females	Clonidine	Propranolol	-0.6 (-14.1 to 12.9)
% females	Clonidine	Rofecoxib	-7.0 (-39.7 to 25.7)
% females	Clonidine	Telmisartan	-7.0 (-39.7 to 25.7)
% females	Clonidine	Timolol	5.8 (-18.2 to 29.8)
% females	Clonidine	Tizanidine	-1.5 (-34.2 to 31.2)
% females	Clonidine	Tolfenamic Acid	-9.5 (-42.2 to 23.2)
% females	Clonidine	Tonabersat	-14.8 (-47.5 to 17.9)
% females	Clonidine	Topiramate	7.5 (-6.4 to 21.4)
% females	Clonidine	Valproate	-5.2 (-29.2 to 18.9)
% females	Clonidine	Verapamil	-3.0 (-27.0 to 21.0)
% females	Clonidine	Vigabatrin	3.6 (-29.1 to 36.3)
% females	Dihydroergocryptine	Dihydroergotamine	1.4 (-34.9 to 37.7)
% females	Dihydroergocryptine	Divalproex	-6.7 (-45.2 to 31.8)
% females	Dihydroergocryptine	Femoxetine	-10.6 (-46.9 to 25.7)
% females	Dihydroergocryptine	Fluoxetine	-5.8 (-41.0 to 29.3)
% females	Dihydroergocryptine	Gabapentin	-3.1 (-39.4 to 33.2)
% females	Dihydroergocryptine	Guanfacine	-12.4 (-56.9 to 32.1)
% females	Dihydroergocryptine	Indobufen	3.6 (-40.9 to 48.1)
% females	Dihydroergocryptine	Indomethacin	-4.4 (-48.9 to 40.1)
% females	Dihydroergocryptine	Induprofen	11.6 (-32.9 to 56.1)
% females	Dihydroergocryptine	Ketoprofen	-16.4 (-60.9 to 28.1)
% females	Dihydroergocryptine	Lamotrigine	-10.2 (-54.7 to 34.3)
% females	Dihydroergocryptine	Lisinopril	-9.4 (-53.9 to 35.1)
% females	Dihydroergocryptine	Methysergide	-8.4 (-52.9 to 36.1)
% females	Dihydroergocryptine	Metoprolol	-11.5 (-47.8 to 24.8)
% females	Dihydroergocryptine	Magnesium	-17.9 (-56.4 to 20.6)
% females	Dihydroergocryptine	Montelukast	-16.4 (-60.9 to 28.1)
% females	Dihydroergocryptine	Nadolol	-9.7 (-54.2 to 34.8)
% females	Dihydroergocryptine	Naproxen sodium	-7.7 (-44.0 to 28.6)
% females	Dihydroergocryptine	Nicardipine	-1.4 (-45.9 to 43.1)
% females	Dihydroergocryptine	Nifedipine	-7.4 (-51.9 to 37.1)
% females	Dihydroergocryptine	Nimodipine	1.3 (-35.0 to 37.6)
% females	Dihydroergocryptine	Oxcarbazepine	-13.1 (-57.6 to 31.4)
% females	Dihydroergocryptine	Pindolol	-14.1 (-58.6 to 30.4)
% females	Dihydroergocryptine	Propranolol	-6.5 (-39.5 to 26.5)
% females	Dihydroergocryptine	Rofecoxib	-12.9 (-57.4 to 31.6)
% females	Dihydroergocryptine	Telmisartan	-12.9 (-57.4 to 31.6)
% females	Dihydroergocryptine	Timolol	-0.1 (-38.6 to 38.4)
% females	Dihydroergocryptine	Tizanidine	-7.4 (-51.9 to 37.1)
% females	Dihydroergocryptine	Tolfenamic Acid	-15.4 (-59.9 to 29.1)
% females	Dihydroergocryptine	Tonabersat	-20.7 (-65.2 to 23.8)
% females	Dihydroergocryptine	Topiramate	1.6 (-31.6 to 34.7)
% females	Dihydroergocryptine	Valproate	-11.1 (-49.6 to 27.5)
% females	Dihydroergocryptine	Verapamil	-8.9 (-47.4 to 29.6)
% females	Dihydroergocryptine	Vigabatrin	-2.3 (-46.8 to 42.2)
% females	Dihydroergotamine	Divalproex	-8.1 (-36.8 to 20.6)
% females	Dihydroergotamine	Femoxetine	-12.0 (-37.6 to 13.7)
% females	Dihydroergotamine	Fluoxetine	-7.2 (-31.2 to 16.8)
% females	Dihydroergotamine	Gabapentin	-4.5 (-30.1 to 21.2)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Dihydroergotamine	Guanfacine	-13.8 (-50.1 to 22.5)
% females	Dihydroergotamine	Indobufen	2.2 (-34.1 to 38.5)
% females	Dihydroergotamine	Indomethacin	-5.8 (-42.1 to 30.5)
% females	Dihydroergotamine	Induprofen	10.2 (-26.1 to 46.5)
% females	Dihydroergotamine	Ketoprofen	-17.8 (-54.1 to 18.5)
% females	Dihydroergotamine	Lamotrigine	-11.6 (-47.9 to 24.7)
% females	Dihydroergotamine	Lisinopril	-10.8 (-47.1 to 25.5)
% females	Dihydroergotamine	Methysergide	-9.8 (-46.1 to 26.5)
% females	Dihydroergotamine	Metoprolol	-12.8 (-38.5 to 12.8)
% females	Dihydroergotamine	Magnesium	-19.3 (-48.0 to 9.4)
% females	Dihydroergotamine	Montelukast	-17.8 (-54.1 to 18.5)
% females	Dihydroergotamine	Nadolol	-11.1 (-47.4 to 25.2)
% females	Dihydroergotamine	Naproxen sodium	-9.1 (-34.8 to 16.6)
% females	Dihydroergotamine	Nicardipine	-2.8 (-39.1 to 33.5)
% females	Dihydroergotamine	Nifedipine	-8.8 (-45.1 to 27.5)
% females	Dihydroergotamine	Nimodipine	-0.1 (-25.8 to 25.6)
% females	Dihydroergotamine	Oxcarbazepine	-14.5 (-50.8 to 21.8)
% females	Dihydroergotamine	Pindolol	-15.5 (-51.8 to 20.8)
% females	Dihydroergotamine	Propranolol	-7.9 (-28.6 to 12.8)
% females	Dihydroergotamine	Rofecoxib	-14.3 (-50.6 to 22.0)
% females	Dihydroergotamine	Telmisartan	-14.3 (-50.6 to 22.0)
% females	Dihydroergotamine	Timolol	-1.5 (-30.2 to 27.2)
% females	Dihydroergotamine	Tizanidine	-8.8 (-45.1 to 27.5)
% females	Dihydroergotamine	Tolfenamic Acid	-16.8 (-53.1 to 19.5)
% females	Dihydroergotamine	Tonabersat	-22.1 (-58.4 to 14.2)
% females	Dihydroergotamine	Topiramate	0.2 (-20.7 to 21.2)
% females	Dihydroergotamine	Valproate	-12.4 (-41.1 to 16.3)
% females	Dihydroergotamine	Verapamil	-10.3 (-39.0 to 18.4)
% females	Dihydroergotamine	Vigabatrin	-3.7 (-40.0 to 32.6)
% females	Divalproex	Femoxetine	-3.9 (-32.6 to 24.8)
% females	Divalproex	Fluoxetine	0.9 (-26.4 to 28.1)
% females	Divalproex	Gabapentin	3.6 (-25.1 to 32.3)
% females	Divalproex	Guanfacine	-5.7 (-44.2 to 32.8)
% females	Divalproex	Indobufen	10.3 (-28.2 to 48.8)
% females	Divalproex	Indomethacin	2.3 (-36.2 to 40.8)
% females	Divalproex	Induprofen	18.3 (-20.2 to 56.8)
% females	Divalproex	Ketoprofen	-9.7 (-48.2 to 28.8)
% females	Divalproex	Lamotrigine	-3.5 (-42.0 to 35.0)
% females	Divalproex	Lisinopril	-2.7 (-41.2 to 35.8)
% females	Divalproex	Methysergide	-1.7 (-40.2 to 36.8)
% females	Divalproex	Metoprolol	-4.8 (-33.5 to 23.9)
% females	Divalproex	Magnesium	-11.2 (-42.6 to 20.2)
% females	Divalproex	Montelukast	-9.7 (-48.2 to 28.8)
% females	Divalproex	Nadolol	-3.0 (-41.5 to 35.5)
% females	Divalproex	Naproxen sodium	-1.0 (-29.7 to 27.7)
% females	Divalproex	Nicardipine	5.3 (-33.2 to 43.8)
% females	Divalproex	Nifedipine	-0.7 (-39.2 to 37.8)
% females	Divalproex	Nimodipine	8.0 (-20.7 to 36.7)
% females	Divalproex	Oxcarbazepine	-6.4 (-44.9 to 32.1)
% females	Divalproex	Pindolol	-7.4 (-45.9 to 31.1)
% females	Divalproex	Propranolol	0.2 (-24.2 to 24.6)
% females	Divalproex	Rofecoxib	-6.2 (-44.7 to 32.3)
% females	Divalproex	Telmisartan	-6.2 (-44.7 to 32.3)
% females	Divalproex	Timolol	6.6 (-24.8 to 38.0)
% females	Divalproex	Tizanidine	-0.7 (-39.2 to 37.8)
% females	Divalproex	Tolfenamic Acid	-8.7 (-47.2 to 29.8)
% females	Divalproex	Tonabersat	-14.0 (-52.5 to 24.5)
% females	Divalproex	Topiramate	8.3 (-16.3 to 32.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Divalproex	Valproate	-4.4 (-35.8 to 27.1)
% females	Divalproex	Verapamil	-2.2 (-33.6 to 29.2)
% females	Divalproex	Vigabatrin	4.4 (-34.1 to 42.9)
% females	Femoxetine	Fluoxetine	4.8 (-19.2 to 28.8)
% females	Femoxetine	Gabapentin	7.5 (-18.2 to 33.2)
% females	Femoxetine	Guanfacine	-1.8 (-38.1 to 34.5)
% females	Femoxetine	Indobufen	14.2 (-22.1 to 50.5)
% females	Femoxetine	Indomethacin	6.2 (-30.1 to 42.5)
% females	Femoxetine	Induprofen	22.2 (-14.1 to 58.5)
% females	Femoxetine	Ketoprofen	-5.8 (-42.1 to 30.5)
% females	Femoxetine	Lamotrigine	0.4 (-35.9 to 36.7)
% females	Femoxetine	Lisinopril	1.2 (-35.1 to 37.5)
% females	Femoxetine	Methysergide	2.2 (-34.1 to 38.5)
% females	Femoxetine	Metoprolol	-0.9 (-26.5 to 24.8)
% females	Femoxetine	Magnesium	-7.3 (-36.0 to 21.4)
% females	Femoxetine	Montelukast	-5.8 (-42.1 to 30.5)
% females	Femoxetine	Nadolol	0.9 (-35.4 to 37.2)
% females	Femoxetine	Naproxen sodium	2.9 (-22.8 to 28.5)
% females	Femoxetine	Nicardipine	9.2 (-27.1 to 45.5)
% females	Femoxetine	Nifedipine	3.2 (-33.1 to 39.5)
% females	Femoxetine	Nimodipine	11.9 (-13.8 to 37.5)
% females	Femoxetine	Oxcarbazepine	-2.5 (-38.8 to 33.8)
% females	Femoxetine	Pindolol	-3.5 (-39.8 to 32.8)
% females	Femoxetine	Propranolol	4.1 (-16.6 to 24.8)
% females	Femoxetine	Rofecoxib	-2.3 (-38.6 to 34.0)
% females	Femoxetine	Telmisartan	-2.3 (-38.6 to 34.0)
% females	Femoxetine	Timolol	10.5 (-18.2 to 39.2)
% females	Femoxetine	Tizanidine	3.2 (-33.1 to 39.5)
% females	Femoxetine	Tolfenamic Acid	-4.8 (-41.1 to 31.5)
% females	Femoxetine	Tonabersat	-10.1 (-46.4 to 26.2)
% females	Femoxetine	Topiramate	12.2 (-8.8 to 33.2)
% females	Femoxetine	Valproate	-0.5 (-29.2 to 28.3)
% females	Femoxetine	Verapamil	1.7 (-27.0 to 30.4)
% females	Femoxetine	Vigabatrin	8.3 (-28.0 to 44.6)
% females	Fluoxetine	Gabapentin	2.7 (-21.3 to 26.7)
% females	Fluoxetine	Guanfacine	-6.6 (-41.7 to 28.6)
% females	Fluoxetine	Indobufen	9.4 (-25.7 to 44.6)
% females	Fluoxetine	Indomethacin	1.4 (-33.7 to 36.6)
% females	Fluoxetine	Induprofen	17.4 (-17.7 to 52.6)
% females	Fluoxetine	Ketoprofen	-10.6 (-45.7 to 24.6)
% females	Fluoxetine	Lamotrigine	-4.4 (-39.5 to 30.8)
% females	Fluoxetine	Lisinopril	-3.6 (-38.7 to 31.6)
% females	Fluoxetine	Methysergide	-2.6 (-37.7 to 32.6)
% females	Fluoxetine	Metoprolol	-5.6 (-29.7 to 18.4)
% females	Fluoxetine	Magnesium	-12.1 (-39.3 to 15.2)
% females	Fluoxetine	Montelukast	-10.6 (-45.7 to 24.6)
% females	Fluoxetine	Nadolol	-3.9 (-39.0 to 31.3)
% females	Fluoxetine	Naproxen sodium	-1.9 (-25.9 to 22.1)
% females	Fluoxetine	Nicardipine	4.4 (-30.7 to 39.6)
% females	Fluoxetine	Nifedipine	-1.6 (-36.7 to 33.6)
% females	Fluoxetine	Nimodipine	7.1 (-16.9 to 31.1)
% females	Fluoxetine	Oxcarbazepine	-7.3 (-42.4 to 27.9)
% females	Fluoxetine	Pindolol	-8.3 (-43.4 to 26.9)
% females	Fluoxetine	Propranolol	-0.7 (-19.3 to 17.9)
% females	Fluoxetine	Rofecoxib	-7.1 (-42.2 to 28.1)
% females	Fluoxetine	Telmisartan	-7.1 (-42.2 to 28.1)
% females	Fluoxetine	Timolol	5.7 (-21.5 to 33.0)
% females	Fluoxetine	Tizanidine	-1.6 (-36.7 to 33.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Fluoxetine	Tolfenamic Acid	-9.6 (-44.7 to 25.6)
% females	Fluoxetine	Tonabersat	-14.9 (-50.0 to 20.3)
% females	Fluoxetine	Topiramate	7.4 (-11.5 to 26.3)
% females	Fluoxetine	Valproate	-5.2 (-32.5 to 22.0)
% females	Fluoxetine	Verapamil	-3.1 (-30.3 to 24.2)
% females	Fluoxetine	Vigabatrin	3.5 (-31.6 to 38.7)
% females	Gabapentin	Guanfacine	-9.3 (-45.6 to 27.0)
% females	Gabapentin	Indobufen	6.7 (-29.6 to 43.0)
% females	Gabapentin	Indomethacin	-1.3 (-37.6 to 35.0)
% females	Gabapentin	Induprofen	14.7 (-21.6 to 51.0)
% females	Gabapentin	Ketoprofen	-13.3 (-49.6 to 23.0)
% females	Gabapentin	Lamotrigine	-7.1 (-43.4 to 29.2)
% females	Gabapentin	Lisinopril	-6.3 (-42.6 to 30.0)
% females	Gabapentin	Methysergide	-5.3 (-41.6 to 31.0)
% females	Gabapentin	Metoprolol	-8.4 (-34.0 to 17.3)
% females	Gabapentin	Magnesium	-14.8 (-43.5 to 13.9)
% females	Gabapentin	Montelukast	-13.3 (-49.6 to 23.0)
% females	Gabapentin	Nadolol	-6.6 (-42.9 to 29.7)
% females	Gabapentin	Naproxen sodium	-4.6 (-30.3 to 21.0)
% females	Gabapentin	Nicardipine	1.7 (-34.6 to 38.0)
% females	Gabapentin	Nifedipine	-4.3 (-40.6 to 32.0)
% females	Gabapentin	Nimodipine	4.4 (-21.3 to 30.0)
% females	Gabapentin	Oxcarbazepine	-10.0 (-46.3 to 26.3)
% females	Gabapentin	Pindolol	-11.0 (-47.3 to 25.3)
% females	Gabapentin	Propranolol	-3.4 (-24.1 to 17.3)
% females	Gabapentin	Rofecoxib	-9.8 (-46.1 to 26.5)
% females	Gabapentin	Telmisartan	-9.8 (-46.1 to 26.5)
% females	Gabapentin	Timolol	3.0 (-25.7 to 31.7)
% females	Gabapentin	Tizanidine	-4.3 (-40.6 to 32.0)
% females	Gabapentin	Tolfenamic Acid	-12.3 (-48.6 to 24.0)
% females	Gabapentin	Tonabersat	-17.6 (-53.9 to 18.7)
% females	Gabapentin	Topiramate	4.7 (-16.3 to 25.7)
% females	Gabapentin	Valproate	-8.0 (-36.7 to 20.8)
% females	Gabapentin	Verapamil	-5.8 (-34.5 to 22.9)
% females	Gabapentin	Vigabatrin	0.8 (-35.5 to 37.1)
% females	Guanfacine	Indobufen	16.0 (-28.5 to 60.5)
% females	Guanfacine	Indomethacin	8.0 (-36.5 to 52.5)
% females	Guanfacine	Induprofen	24.0 (-20.5 to 68.5)
% females	Guanfacine	Ketoprofen	-4.0 (-48.5 to 40.5)
% females	Guanfacine	Lamotrigine	2.2 (-42.3 to 46.7)
% females	Guanfacine	Lisinopril	3.0 (-41.5 to 47.5)
% females	Guanfacine	Methysergide	4.0 (-40.5 to 48.5)
% females	Guanfacine	Metoprolol	0.9 (-35.4 to 37.2)
% females	Guanfacine	Magnesium	-5.5 (-44.0 to 33.0)
% females	Guanfacine	Montelukast	-4.0 (-48.5 to 40.5)
% females	Guanfacine	Nadolol	2.7 (-41.8 to 47.2)
% females	Guanfacine	Naproxen sodium	4.7 (-31.6 to 41.0)
% females	Guanfacine	Nicardipine	11.0 (-33.5 to 55.5)
% females	Guanfacine	Nifedipine	5.0 (-39.5 to 49.5)
% females	Guanfacine	Nimodipine	13.7 (-22.6 to 50.0)
% females	Guanfacine	Oxcarbazepine	-0.7 (-45.2 to 43.8)
% females	Guanfacine	Pindolol	-1.7 (-46.2 to 42.8)
% females	Guanfacine	Propranolol	5.9 (-27.1 to 38.9)
% females	Guanfacine	Rofecoxib	-0.5 (-45.0 to 44.0)
% females	Guanfacine	Telmisartan	-0.5 (-45.0 to 44.0)
% females	Guanfacine	Timolol	12.3 (-26.2 to 50.8)
% females	Guanfacine	Tizanidine	5.0 (-39.5 to 49.5)
% females	Guanfacine	Tolfenamic Acid	-3.0 (-47.5 to 41.5)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Guanfacine	Tonabersat	-8.3 (-52.8 to 36.2)
% females	Guanfacine	Topiramate	14.0 (-19.2 to 47.1)
% females	Guanfacine	Valproate	1.4 (-37.2 to 39.9)
% females	Guanfacine	Verapamil	3.5 (-35.0 to 42.0)
% females	Guanfacine	Vigabatrin	10.1 (-34.4 to 54.6)
% females	Indobufen	Indomethacin	-8.0 (-52.5 to 36.5)
% females	Indobufen	Induprofen	8.0 (-36.5 to 52.5)
% females	Indobufen	Ketoprofen	-20.0 (-64.5 to 24.5)
% females	Indobufen	Lamotrigine	-13.8 (-58.3 to 30.7)
% females	Indobufen	Lisinopril	-13.0 (-57.5 to 31.5)
% females	Indobufen	Methysergide	-12.0 (-56.5 to 32.5)
% females	Indobufen	Metoprolol	-15.1 (-51.4 to 21.2)
% females	Indobufen	Magnesium	-21.5 (-60.0 to 17.0)
% females	Indobufen	Montelukast	-20.0 (-64.5 to 24.5)
% females	Indobufen	Nadolol	-13.3 (-57.8 to 31.2)
% females	Indobufen	Naproxen sodium	-11.3 (-47.6 to 25.0)
% females	Indobufen	Nicardipine	-5.0 (-49.5 to 39.5)
% females	Indobufen	Nifedipine	-11.0 (-55.5 to 33.5)
% females	Indobufen	Nimodipine	-2.3 (-38.6 to 34.0)
% females	Indobufen	Oxcarbazepine	-16.7 (-61.2 to 27.8)
% females	Indobufen	Pindolol	-17.7 (-62.2 to 26.8)
% females	Indobufen	Propranolol	-10.1 (-43.1 to 22.9)
% females	Indobufen	Rofecoxib	-16.5 (-61.0 to 28.0)
% females	Indobufen	Telmisartan	-16.5 (-61.0 to 28.0)
% females	Indobufen	Timolol	-3.7 (-42.2 to 34.8)
% females	Indobufen	Tizanidine	-11.0 (-55.5 to 33.5)
% females	Indobufen	Tolfenamic Acid	-19.0 (-63.5 to 25.5)
% females	Indobufen	Tonabersat	-24.3 (-68.8 to 20.2)
% females	Indobufen	Topiramate	-2.0 (-35.2 to 31.1)
% females	Indobufen	Valproate	-14.7 (-53.2 to 23.9)
% females	Indobufen	Verapamil	-12.5 (-51.0 to 26.0)
% females	Indobufen	Vigabatrin	-5.9 (-50.4 to 38.6)
% females	Indomethacin	Induprofen	16.0 (-28.5 to 60.5)
% females	Indomethacin	Ketoprofen	-12.0 (-56.5 to 32.5)
% females	Indomethacin	Lamotrigine	-5.8 (-50.3 to 38.7)
% females	Indomethacin	Lisinopril	-5.0 (-49.5 to 39.5)
% females	Indomethacin	Methysergide	-4.0 (-48.5 to 40.5)
% females	Indomethacin	Metoprolol	-7.1 (-43.4 to 29.2)
% females	Indomethacin	Magnesium	-13.5 (-52.0 to 25.0)
% females	Indomethacin	Montelukast	-12.0 (-56.5 to 32.5)
% females	Indomethacin	Nadolol	-5.3 (-49.8 to 39.2)
% females	Indomethacin	Naproxen sodium	-3.3 (-39.6 to 33.0)
% females	Indomethacin	Nicardipine	3.0 (-41.5 to 47.5)
% females	Indomethacin	Nifedipine	-3.0 (-47.5 to 41.5)
% females	Indomethacin	Nimodipine	5.7 (-30.6 to 42.0)
% females	Indomethacin	Oxcarbazepine	-8.7 (-53.2 to 35.8)
% females	Indomethacin	Pindolol	-9.7 (-54.2 to 34.8)
% females	Indomethacin	Propranolol	-2.1 (-35.1 to 30.9)
% females	Indomethacin	Rofecoxib	-8.5 (-53.0 to 36.0)
% females	Indomethacin	Telmisartan	-8.5 (-53.0 to 36.0)
% females	Indomethacin	Timolol	4.3 (-34.2 to 42.8)
% females	Indomethacin	Tizanidine	-3.0 (-47.5 to 41.5)
% females	Indomethacin	Tolfenamic Acid	-11.0 (-55.5 to 33.5)
% females	Indomethacin	Tonabersat	-16.3 (-60.8 to 28.2)
% females	Indomethacin	Topiramate	6.0 (-27.2 to 39.1)
% females	Indomethacin	Valproate	-6.7 (-45.2 to 31.9)
% females	Indomethacin	Verapamil	-4.5 (-43.0 to 34.0)
% females	Indomethacin	Vigabatrin	2.1 (-42.4 to 46.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Induprofen	Ketoprofen	-28.0 (-72.5 to 16.5)
% females	Induprofen	Lamotrigine	-21.8 (-66.3 to 22.7)
% females	Induprofen	Lisinopril	-21.0 (-65.5 to 23.5)
% females	Induprofen	Methysergide	-20.0 (-64.5 to 24.5)
% females	Induprofen	Metoprolol	-23.1 (-59.4 to 13.2)
% females	Induprofen	Magnesium	-29.5 (-68.0 to 9.0)
% females	Induprofen	Montelukast	-28.0 (-72.5 to 16.5)
% females	Induprofen	Nadolol	-21.3 (-65.8 to 23.2)
% females	Induprofen	Naproxen sodium	-19.3 (-55.6 to 17.0)
% females	Induprofen	Nicardipine	-13.0 (-57.5 to 31.5)
% females	Induprofen	Nifedipine	-19.0 (-63.5 to 25.5)
% females	Induprofen	Nimodipine	-10.3 (-46.6 to 26.0)
% females	Induprofen	Oxcarbazepine	-24.7 (-69.2 to 19.8)
% females	Induprofen	Pindolol	-25.7 (-70.2 to 18.8)
% females	Induprofen	Propranolol	-18.1 (-51.1 to 14.9)
% females	Induprofen	Rofecoxib	-24.5 (-69.0 to 20.0)
% females	Induprofen	Telmisartan	-24.5 (-69.0 to 20.0)
% females	Induprofen	Timolol	-11.7 (-50.2 to 26.8)
% females	Induprofen	Tizanidine	-19.0 (-63.5 to 25.5)
% females	Induprofen	Tolfenamic Acid	-27.0 (-71.5 to 17.5)
% females	Induprofen	Tonabersat	-32.3 (-76.8 to 12.2)
% females	Induprofen	Topiramate	-10.0 (-43.2 to 23.1)
% females	Induprofen	Valproate	-22.7 (-61.2 to 15.9)
% females	Induprofen	Verapamil	-20.5 (-59.0 to 18.0)
% females	Induprofen	Vigabatrin	-13.9 (-58.4 to 30.6)
% females	Ketoprofen	Lamotrigine	6.2 (-38.3 to 50.7)
% females	Ketoprofen	Lisinopril	7.0 (-37.5 to 51.5)
% females	Ketoprofen	Methysergide	8.0 (-36.5 to 52.5)
% females	Ketoprofen	Metoprolol	4.9 (-31.4 to 41.2)
% females	Ketoprofen	Magnesium	-1.5 (-40.0 to 37.0)
% females	Ketoprofen	Montelukast	0.0 (-44.5 to 44.5)
% females	Ketoprofen	Nadolol	6.7 (-37.8 to 51.2)
% females	Ketoprofen	Naproxen sodium	8.7 (-27.6 to 45.0)
% females	Ketoprofen	Nicardipine	15.0 (-29.5 to 59.5)
% females	Ketoprofen	Nifedipine	9.0 (-35.5 to 53.5)
% females	Ketoprofen	Nimodipine	17.7 (-18.6 to 54.0)
% females	Ketoprofen	Oxcarbazepine	3.3 (-41.2 to 47.8)
% females	Ketoprofen	Pindolol	2.3 (-42.2 to 46.8)
% females	Ketoprofen	Propranolol	9.9 (-23.1 to 42.9)
% females	Ketoprofen	Rofecoxib	3.5 (-41.0 to 48.0)
% females	Ketoprofen	Telmisartan	3.5 (-41.0 to 48.0)
% females	Ketoprofen	Timolol	16.3 (-22.2 to 54.8)
% females	Ketoprofen	Tizanidine	9.0 (-35.5 to 53.5)
% females	Ketoprofen	Tolfenamic Acid	1.0 (-43.5 to 45.5)
% females	Ketoprofen	Tonabersat	-4.3 (-48.8 to 40.2)
% females	Ketoprofen	Topiramate	18.0 (-15.2 to 51.1)
% females	Ketoprofen	Valproate	5.4 (-33.2 to 43.9)
% females	Ketoprofen	Verapamil	7.5 (-31.0 to 46.0)
% females	Ketoprofen	Vigabatrin	14.1 (-30.4 to 58.6)
% females	Lamotrigine	Lisinopril	0.8 (-43.7 to 45.3)
% females	Lamotrigine	Methysergide	1.8 (-42.7 to 46.3)
% females	Lamotrigine	Metoprolol	-1.3 (-37.6 to 35.0)
% females	Lamotrigine	Magnesium	-7.7 (-46.2 to 30.8)
% females	Lamotrigine	Montelukast	-6.2 (-50.7 to 38.3)
% females	Lamotrigine	Nadolol	0.5 (-44.0 to 45.0)
% females	Lamotrigine	Naproxen sodium	2.5 (-33.8 to 38.8)
% females	Lamotrigine	Nicardipine	8.8 (-35.7 to 53.3)
% females	Lamotrigine	Nifedipine	2.8 (-41.7 to 47.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Lamotrigine	Nimodipine	11.5 (-24.8 to 47.8)
% females	Lamotrigine	Oxcarbazepine	-2.9 (-47.4 to 41.6)
% females	Lamotrigine	Pindolol	-3.9 (-48.4 to 40.6)
% females	Lamotrigine	Propranolol	3.7 (-29.3 to 36.7)
% females	Lamotrigine	Rofecoxib	-2.7 (-47.2 to 41.8)
% females	Lamotrigine	Telmisartan	-2.7 (-47.2 to 41.8)
% females	Lamotrigine	Timolol	10.1 (-28.4 to 48.6)
% females	Lamotrigine	Tizanidine	2.8 (-41.7 to 47.3)
% females	Lamotrigine	Tolfenamic Acid	-5.2 (-49.7 to 39.3)
% females	Lamotrigine	Tonabersat	-10.5 (-55.0 to 34.0)
% females	Lamotrigine	Topiramate	11.8 (-21.4 to 44.9)
% females	Lamotrigine	Valproate	-0.9 (-39.4 to 37.7)
% females	Lamotrigine	Verapamil	1.3 (-37.2 to 39.8)
% females	Lamotrigine	Vigabatrin	7.9 (-36.6 to 52.4)
% females	Lisinopril	Methysergide	1.0 (-43.5 to 45.5)
% females	Lisinopril	Metoprolol	-2.1 (-38.4 to 34.2)
% females	Lisinopril	Magnesium	-8.5 (-47.0 to 30.0)
% females	Lisinopril	Montelukast	-7.0 (-51.5 to 37.5)
% females	Lisinopril	Nadolol	-0.3 (-44.8 to 44.2)
% females	Lisinopril	Naproxen sodium	1.7 (-34.6 to 38.0)
% females	Lisinopril	Nicardipine	8.0 (-36.5 to 52.5)
% females	Lisinopril	Nifedipine	2.0 (-42.5 to 46.5)
% females	Lisinopril	Nimodipine	10.7 (-25.6 to 47.0)
% females	Lisinopril	Oxcarbazepine	-3.7 (-48.2 to 40.8)
% females	Lisinopril	Pindolol	-4.7 (-49.2 to 39.8)
% females	Lisinopril	Propranolol	2.9 (-30.1 to 35.9)
% females	Lisinopril	Rofecoxib	-3.5 (-48.0 to 41.0)
% females	Lisinopril	Telmisartan	-3.5 (-48.0 to 41.0)
% females	Lisinopril	Timolol	9.3 (-29.2 to 47.8)
% females	Lisinopril	Tizanidine	2.0 (-42.5 to 46.5)
% females	Lisinopril	Tolfenamic Acid	-6.0 (-50.5 to 38.5)
% females	Lisinopril	Tonabersat	-11.3 (-55.8 to 33.2)
% females	Lisinopril	Topiramate	11.0 (-22.2 to 44.1)
% females	Lisinopril	Valproate	-1.7 (-40.2 to 36.9)
% females	Lisinopril	Verapamil	0.5 (-38.0 to 39.0)
% females	Lisinopril	Vigabatrin	7.1 (-37.4 to 51.6)
% females	Magnesium	Montelukast	1.5 (-37.0 to 40.0)
% females	Magnesium	Nadolol	8.2 (-30.3 to 46.7)
% females	Magnesium	Naproxen sodium	10.2 (-18.5 to 38.9)
% females	Magnesium	Nicardipine	16.5 (-22.0 to 55.0)
% females	Magnesium	Nifedipine	10.5 (-28.0 to 49.0)
% females	Magnesium	Nimodipine	19.2 (-9.5 to 47.9)
% females	Magnesium	Oxcarbazepine	4.8 (-33.7 to 43.3)
% females	Magnesium	Pindolol	3.8 (-34.7 to 42.3)
% females	Magnesium	Propranolol	11.4 (-13.0 to 35.8)
% females	Magnesium	Rofecoxib	5.0 (-33.5 to 43.5)
% females	Magnesium	Telmisartan	5.0 (-33.5 to 43.5)
% females	Magnesium	Timolol	17.8 (-13.6 to 49.2)
% females	Magnesium	Tizanidine	10.5 (-28.0 to 49.0)
% females	Magnesium	Tolfenamic Acid	2.5 (-36.0 to 41.0)
% females	Magnesium	Tonabersat	-2.8 (-41.3 to 35.7)
% females	Magnesium	Topiramate	19.5 (-5.1 to 44.1)
% females	Magnesium	Valproate	6.9 (-24.6 to 38.3)
% females	Magnesium	Verapamil	9.0 (-22.4 to 40.4)
% females	Magnesium	Vigabatrin	15.6 (-22.9 to 54.1)
% females	Methysergide	Metoprolol	-3.1 (-39.4 to 33.2)
% females	Methysergide	Magnesium	-9.5 (-48.0 to 29.0)
% females	Methysergide	Montelukast	-8.0 (-52.5 to 36.5)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Methysergide	Nadolol	-1.3 (-45.8 to 43.2)
% females	Methysergide	Naproxen sodium	0.7 (-35.6 to 37.0)
% females	Methysergide	Nicardipine	7.0 (-37.5 to 51.5)
% females	Methysergide	Nifedipine	1.0 (-43.5 to 45.5)
% females	Methysergide	Nimodipine	9.7 (-26.6 to 46.0)
% females	Methysergide	Oxcarbazepine	-4.7 (-49.2 to 39.8)
% females	Methysergide	Pindolol	-5.7 (-50.2 to 38.8)
% females	Methysergide	Propranolol	1.9 (-31.1 to 34.9)
% females	Methysergide	Rofecoxib	-4.5 (-49.0 to 40.0)
% females	Methysergide	Telmisartan	-4.5 (-49.0 to 40.0)
% females	Methysergide	Timolol	8.3 (-30.2 to 46.8)
% females	Methysergide	Tizanidine	1.0 (-43.5 to 45.5)
% females	Methysergide	Tolfenamic Acid	-7.0 (-51.5 to 37.5)
% females	Methysergide	Tonabersat	-12.3 (-56.8 to 32.2)
% females	Methysergide	Topiramate	10.0 (-23.2 to 43.1)
% females	Methysergide	Valproate	-2.7 (-41.2 to 35.9)
% females	Methysergide	Verapamil	-0.5 (-39.0 to 38.0)
% females	Methysergide	Vigabatrin	6.1 (-38.4 to 50.6)
% females	Metoprolol	Magnesium	-6.4 (-35.1 to 22.3)
% females	Metoprolol	Montelukast	-4.9 (-41.2 to 31.4)
% females	Metoprolol	Nadolol	1.8 (-34.5 to 38.1)
% females	Metoprolol	Naproxen sodium	3.7 (-21.9 to 29.4)
% females	Metoprolol	Nicardipine	10.1 (-26.2 to 46.4)
% females	Metoprolol	Nifedipine	4.1 (-32.2 to 40.4)
% females	Metoprolol	Nimodipine	12.7 (-12.9 to 38.4)
% females	Metoprolol	Oxcarbazepine	-1.6 (-37.9 to 34.7)
% females	Metoprolol	Pindolol	-2.6 (-38.9 to 33.7)
% females	Metoprolol	Propranolol	5.0 (-15.7 to 25.7)
% females	Metoprolol	Rofecoxib	-1.4 (-37.7 to 34.9)
% females	Metoprolol	Telmisartan	-1.4 (-37.7 to 34.9)
% females	Metoprolol	Timolol	11.4 (-17.3 to 40.1)
% females	Metoprolol	Tizanidine	4.1 (-32.2 to 40.4)
% females	Metoprolol	Tolfenamic Acid	-3.9 (-40.2 to 32.4)
% females	Metoprolol	Tonabersat	-9.2 (-45.5 to 27.1)
% females	Metoprolol	Topiramate	13.1 (-7.9 to 34.0)
% females	Metoprolol	Valproate	0.4 (-28.3 to 29.1)
% females	Metoprolol	Verapamil	2.6 (-26.1 to 31.3)
% females	Metoprolol	Vigabatrin	9.2 (-27.1 to 45.5)
% females	Montelukast	Nadolol	6.7 (-37.8 to 51.2)
% females	Montelukast	Naproxen sodium	8.7 (-27.6 to 45.0)
% females	Montelukast	Nicardipine	15.0 (-29.5 to 59.5)
% females	Montelukast	Nifedipine	9.0 (-35.5 to 53.5)
% females	Montelukast	Nimodipine	17.7 (-18.6 to 54.0)
% females	Montelukast	Oxcarbazepine	3.3 (-41.2 to 47.8)
% females	Montelukast	Pindolol	2.3 (-42.2 to 46.8)
% females	Montelukast	Propranolol	9.9 (-23.1 to 42.9)
% females	Montelukast	Rofecoxib	3.5 (-41.0 to 48.0)
% females	Montelukast	Telmisartan	3.5 (-41.0 to 48.0)
% females	Montelukast	Timolol	16.3 (-22.2 to 54.8)
% females	Montelukast	Tizanidine	9.0 (-35.5 to 53.5)
% females	Montelukast	Tolfenamic Acid	1.0 (-43.5 to 45.5)
% females	Montelukast	Tonabersat	-4.3 (-48.8 to 40.2)
% females	Montelukast	Topiramate	18.0 (-15.2 to 51.1)
% females	Montelukast	Valproate	5.4 (-33.2 to 43.9)
% females	Montelukast	Verapamil	7.5 (-31.0 to 46.0)
% females	Montelukast	Vigabatrin	14.1 (-30.4 to 58.6)
% females	Nadolol	Naproxen sodium	2.0 (-34.3 to 38.3)
% females	Nadolol	Nicardipine	8.3 (-36.2 to 52.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Nadolol	Nifedipine	2.3 (-42.2 to 46.8)
% females	Nadolol	Nimodipine	11.0 (-25.3 to 47.3)
% females	Nadolol	Oxcarbazepine	-3.4 (-47.9 to 41.1)
% females	Nadolol	Pindolol	-4.4 (-48.9 to 40.1)
% females	Nadolol	Propranolol	3.2 (-29.8 to 36.2)
% females	Nadolol	Rofecoxib	-3.2 (-47.7 to 41.3)
% females	Nadolol	Telmisartan	-3.2 (-47.7 to 41.3)
% females	Nadolol	Timolol	9.6 (-28.9 to 48.1)
% females	Nadolol	Tizanidine	2.3 (-42.2 to 46.8)
% females	Nadolol	Tolfenamic Acid	-5.7 (-50.2 to 38.8)
% females	Nadolol	Tonabersat	-11.0 (-55.5 to 33.5)
% females	Nadolol	Topiramate	11.3 (-21.9 to 44.4)
% females	Nadolol	Valproate	-1.4 (-39.9 to 37.2)
% females	Nadolol	Verapamil	0.8 (-37.7 to 39.3)
% females	Nadolol	Vigabatrin	7.4 (-37.1 to 51.9)
% females	Naproxen sodium	Nicardipine	6.3 (-30.0 to 42.6)
% females	Naproxen sodium	Nifedipine	0.3 (-36.0 to 36.6)
% females	Naproxen sodium	Nimodipine	9.0 (-16.7 to 34.7)
% females	Naproxen sodium	Oxcarbazepine	-5.4 (-41.7 to 30.9)
% females	Naproxen sodium	Pindolol	-6.4 (-42.7 to 29.9)
% females	Naproxen sodium	Propranolol	1.2 (-19.5 to 21.9)
% females	Naproxen sodium	Rofecoxib	-5.2 (-41.5 to 31.1)
% females	Naproxen sodium	Telmisartan	-5.2 (-41.5 to 31.1)
% females	Naproxen sodium	Timolol	7.6 (-21.1 to 36.3)
% females	Naproxen sodium	Tizanidine	0.3 (-36.0 to 36.6)
% females	Naproxen sodium	Tolfenamic Acid	-7.7 (-44.0 to 28.6)
% females	Naproxen sodium	Tonabersat	-13.0 (-49.3 to 23.3)
% females	Naproxen sodium	Topiramate	9.3 (-11.6 to 30.3)
% females	Naproxen sodium	Valproate	-3.3 (-32.0 to 25.4)
% females	Naproxen sodium	Verapamil	-1.2 (-29.9 to 27.5)
% females	Naproxen sodium	Vigabatrin	5.4 (-30.9 to 41.7)
% females	Nicardipine	Nifedipine	-6.0 (-50.5 to 38.5)
% females	Nicardipine	Nimodipine	2.7 (-33.6 to 39.0)
% females	Nicardipine	Oxcarbazepine	-11.7 (-56.2 to 32.8)
% females	Nicardipine	Pindolol	-12.7 (-57.2 to 31.8)
% females	Nicardipine	Propranolol	-5.1 (-38.1 to 27.9)
% females	Nicardipine	Rofecoxib	-11.5 (-56.0 to 33.0)
% females	Nicardipine	Telmisartan	-11.5 (-56.0 to 33.0)
% females	Nicardipine	Timolol	1.3 (-37.2 to 39.8)
% females	Nicardipine	Tizanidine	-6.0 (-50.5 to 38.5)
% females	Nicardipine	Tolfenamic Acid	-14.0 (-58.5 to 30.5)
% females	Nicardipine	Tonabersat	-19.3 (-63.8 to 25.2)
% females	Nicardipine	Topiramate	3.0 (-30.2 to 36.1)
% females	Nicardipine	Valproate	-9.7 (-48.2 to 28.9)
% females	Nicardipine	Verapamil	-7.5 (-46.0 to 31.0)
% females	Nicardipine	Vigabatrin	-0.9 (-45.4 to 43.6)
% females	Nifedipine	Nimodipine	8.7 (-27.6 to 45.0)
% females	Nifedipine	Oxcarbazepine	-5.7 (-50.2 to 38.8)
% females	Nifedipine	Pindolol	-6.7 (-51.2 to 37.8)
% females	Nifedipine	Propranolol	0.9 (-32.1 to 33.9)
% females	Nifedipine	Rofecoxib	-5.5 (-50.0 to 39.0)
% females	Nifedipine	Telmisartan	-5.5 (-50.0 to 39.0)
% females	Nifedipine	Timolol	7.3 (-31.2 to 45.8)
% females	Nifedipine	Tizanidine	0.0 (-44.5 to 44.5)
% females	Nifedipine	Tolfenamic Acid	-8.0 (-52.5 to 36.5)
% females	Nifedipine	Tonabersat	-13.3 (-57.8 to 31.2)
% females	Nifedipine	Topiramate	9.0 (-24.2 to 42.1)
% females	Nifedipine	Valproate	-3.7 (-42.2 to 34.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Nifedipine	Verapamil	-1.5 (-40.0 to 37.0)
% females	Nifedipine	Vigabatrin	5.1 (-39.4 to 49.6)
% females	Nimodipine	Oxcarbazepine	-14.4 (-50.7 to 21.9)
% females	Nimodipine	Pindolol	-15.4 (-51.7 to 20.9)
% females	Nimodipine	Propranolol	-7.8 (-28.5 to 12.9)
% females	Nimodipine	Rofecoxib	-14.2 (-50.5 to 22.1)
% females	Nimodipine	Telmisartan	-14.2 (-50.5 to 22.1)
% females	Nimodipine	Timolol	-1.4 (-30.1 to 27.3)
% females	Nimodipine	Tizanidine	-8.7 (-45.0 to 27.6)
% females	Nimodipine	Tolfenamic Acid	-16.7 (-53.0 to 19.6)
% females	Nimodipine	Tonabersat	-22.0 (-58.3 to 14.3)
% females	Nimodipine	Topiramate	0.3 (-20.6 to 21.3)
% females	Nimodipine	Valproate	-12.3 (-41.0 to 16.4)
% females	Nimodipine	Verapamil	-10.2 (-38.9 to 18.5)
% females	Nimodipine	Vigabatrin	-3.6 (-39.9 to 32.7)
% females	Oxcarbazepine	Pindolol	-1.0 (-45.5 to 43.5)
% females	Oxcarbazepine	Propranolol	6.6 (-26.4 to 39.6)
% females	Oxcarbazepine	Rofecoxib	0.2 (-44.3 to 44.7)
% females	Oxcarbazepine	Telmisartan	0.2 (-44.3 to 44.7)
% females	Oxcarbazepine	Timolol	13.0 (-25.5 to 51.5)
% females	Oxcarbazepine	Tizanidine	5.7 (-38.8 to 50.2)
% females	Oxcarbazepine	Tolfenamic Acid	-2.3 (-46.8 to 42.2)
% females	Oxcarbazepine	Tonabersat	-7.6 (-52.1 to 36.9)
% females	Oxcarbazepine	Topiramate	14.7 (-18.5 to 47.8)
% females	Oxcarbazepine	Valproate	2.1 (-36.5 to 40.6)
% females	Oxcarbazepine	Verapamil	4.2 (-34.3 to 42.7)
% females	Oxcarbazepine	Vigabatrin	10.8 (-33.7 to 55.3)
% females	Pindolol	Propranolol	7.6 (-25.4 to 40.6)
% females	Pindolol	Rofecoxib	1.2 (-43.3 to 45.7)
% females	Pindolol	Telmisartan	1.2 (-43.3 to 45.7)
% females	Pindolol	Timolol	14.0 (-24.5 to 52.5)
% females	Pindolol	Tizanidine	6.7 (-37.8 to 51.2)
% females	Pindolol	Tolfenamic Acid	-1.3 (-45.8 to 43.2)
% females	Pindolol	Tonabersat	-6.6 (-51.1 to 37.9)
% females	Pindolol	Topiramate	15.7 (-17.5 to 48.8)
% females	Pindolol	Valproate	3.1 (-35.5 to 41.6)
% females	Pindolol	Verapamil	5.2 (-33.3 to 43.7)
% females	Pindolol	Vigabatrin	11.8 (-32.7 to 56.3)
% females	Propranolol	Rofecoxib	-6.4 (-39.4 to 26.6)
% females	Propranolol	Telmisartan	-6.4 (-39.4 to 26.6)
% females	Propranolol	Timolol	6.4 (-18.0 to 30.8)
% females	Propranolol	Tizanidine	-0.9 (-33.9 to 32.1)
% females	Propranolol	Tolfenamic Acid	-8.9 (-41.9 to 24.1)
% females	Propranolol	Tonabersat	-14.2 (-47.2 to 18.8)
% females	Propranolol	Topiramate	8.1 (-6.4 to 22.5)
% females	Propranolol	Valproate	-4.5 (-28.9 to 19.8)
% females	Propranolol	Verapamil	-2.4 (-26.8 to 22.0)
% females	Propranolol	Vigabatrin	4.2 (-28.8 to 37.2)
% females	Rofecoxib	Telmisartan	0.0 (-44.5 to 44.5)
% females	Rofecoxib	Timolol	12.8 (-25.7 to 51.3)
% females	Rofecoxib	Tizanidine	5.5 (-39.0 to 50.0)
% females	Rofecoxib	Tolfenamic Acid	-2.5 (-47.0 to 42.0)
% females	Rofecoxib	Tonabersat	-7.8 (-52.3 to 36.7)
% females	Rofecoxib	Topiramate	14.5 (-18.7 to 47.6)
% females	Rofecoxib	Valproate	1.9 (-36.7 to 40.4)
% females	Rofecoxib	Verapamil	4.0 (-34.5 to 42.5)
% females	Rofecoxib	Vigabatrin	10.6 (-33.9 to 55.1)
% females	Telmisartan	Timolol	12.8 (-25.7 to 51.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% females	Telmisartan	Tizanidine	5.5 (-39.0 to 50.0)
% females	Telmisartan	Tolfenamic Acid	-2.5 (-47.0 to 42.0)
% females	Telmisartan	Tonabersat	-7.8 (-52.3 to 36.7)
% females	Telmisartan	Topiramate	14.5 (-18.7 to 47.6)
% females	Telmisartan	Valproate	1.9 (-36.7 to 40.4)
% females	Telmisartan	Verapamil	4.0 (-34.5 to 42.5)
% females	Telmisartan	Vigabatrin	10.6 (-33.9 to 55.1)
% females	Timolol	Tizanidine	-7.3 (-45.8 to 31.2)
% females	Timolol	Tolfenamic Acid	-15.3 (-53.8 to 23.2)
% females	Timolol	Tonabersat	-20.6 (-59.1 to 17.9)
% females	Timolol	Topiramate	1.7 (-22.9 to 26.3)
% females	Timolol	Valproate	-11.0 (-42.4 to 20.5)
% females	Timolol	Verapamil	-8.8 (-40.2 to 22.6)
% females	Timolol	Vigabatrin	-2.2 (-40.7 to 36.3)
% females	Tizanidine	Tolfenamic Acid	-8.0 (-52.5 to 36.5)
% females	Tizanidine	Tonabersat	-13.3 (-57.8 to 31.2)
% females	Tizanidine	Topiramate	9.0 (-24.2 to 42.1)
% females	Tizanidine	Valproate	-3.7 (-42.2 to 34.9)
% females	Tizanidine	Verapamil	-1.5 (-40.0 to 37.0)
% females	Tizanidine	Vigabatrin	5.1 (-39.4 to 49.6)
% females	Tolfenamic Acid	Tonabersat	-5.3 (-49.8 to 39.2)
% females	Tolfenamic Acid	Topiramate	17.0 (-16.2 to 50.1)
% females	Tolfenamic Acid	Valproate	4.4 (-34.2 to 42.9)
% females	Tolfenamic Acid	Verapamil	6.5 (-32.0 to 45.0)
% females	Tolfenamic Acid	Vigabatrin	13.1 (-31.4 to 57.6)
% females	Tonabersat	Topiramate	22.3 (-10.9 to 55.4)
% females	Tonabersat	Valproate	9.7 (-28.9 to 48.2)
% females	Tonabersat	Verapamil	11.8 (-26.7 to 50.3)
% females	Tonabersat	Vigabatrin	18.4 (-26.1 to 62.9)
% females	Topiramate	Valproate	-12.6 (-37.2 to 11.9)
% females	Topiramate	Verapamil	-10.5 (-35.1 to 14.1)
% females	Topiramate	Vigabatrin	-3.9 (-37.0 to 29.3)
% females	Valproate	Verapamil	2.2 (-29.3 to 33.6)
% females	Valproate	Vigabatrin	8.8 (-29.8 to 47.3)
% females	Verapamil	Vigabatrin	6.6 (-31.9 to 45.1)
Obesity, BMI	Acetazolamide	Aspirin	-2.5 (-5.6 to 0.5)
Obesity, BMI	Acetazolamide	Dihydroergotamine	-0.7 (-4.3 to 3.0)
Obesity, BMI	Acetazolamide	Divalproex	-3.7 (-7.9 to 0.5)
Obesity, BMI	Acetazolamide	Gabapentin	-2.6 (-6.8 to 1.6)
Obesity, BMI	Acetazolamide	Nimodipine	0.0 (-4.2 to 4.2)
Obesity, BMI	Acetazolamide	Telmisartan	-1.0 (-5.2 to 3.2)
Obesity, BMI	Acetazolamide	Topiramate	-6.1 (-9.6 to -2.7)
Obesity, BMI	Aspirin	Dihydroergotamine	1.9 (-0.6 to 4.4)
Obesity, BMI	Aspirin	Divalproex	-1.2 (-4.2 to 1.9)
Obesity, BMI	Aspirin	Gabapentin	0.0 (-3.1 to 3.0)
Obesity, BMI	Aspirin	Nimodipine	2.6 (-0.5 to 5.6)
Obesity, BMI	Aspirin	Telmisartan	1.6 (-1.5 to 4.6)
Obesity, BMI	Aspirin	Topiramate	-3.6 (-5.9 to -1.3)
Obesity, BMI	Dihydroergotamine	Divalproex	-3.0 (-6.7 to 0.6)
Obesity, BMI	Dihydroergotamine	Gabapentin	-1.9 (-5.6 to 1.7)
Obesity, BMI	Dihydroergotamine	Nimodipine	0.7 (-3.0 to 4.3)
Obesity, BMI	Dihydroergotamine	Telmisartan	-0.3 (-4.0 to 3.3)
Obesity, BMI	Dihydroergotamine	Topiramate	-5.5 (-8.2 to -2.8)
Obesity, BMI	Divalproex	Gabapentin	1.1 (-3.1 to 5.3)
Obesity, BMI	Divalproex	Nimodipine	3.7 (-0.5 to 7.9)
Obesity, BMI	Divalproex	Telmisartan	2.7 (-1.5 to 6.9)
Obesity, BMI	Divalproex	Topiramate	-2.5 (-5.9 to 1.0)
Obesity, BMI	Gabapentin	Nimodipine	2.6 (-1.6 to 6.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Obesity, BMI	Gabapentin	Telmisartan	1.6 (-2.6 to 5.8)
Obesity, BMI	Gabapentin	Topiramate	-3.6 (-7.0 to -0.1)
Obesity, BMI	Nimodipine	Telmisartan	-1.0 (-5.2 to 3.2)
Obesity, BMI	Nimodipine	Topiramate	-6.2 (-9.6 to -2.7)
Obesity, BMI	Telmisartan	Topiramate	-5.2 (-8.6 to -1.7)
Duration of migraine, years	Atenolol	Clonidine	10.0 (-2.0 to 22.0)
Duration of migraine, years	Atenolol	Dihydroergotamine	10.1 (-2.7 to 22.9)
Duration of migraine, years	Atenolol	Divalproex	3.4 (-9.4 to 16.2)
Duration of migraine, years	Atenolol	Gabapentin	5.2 (-9.5 to 19.9)
Duration of migraine, years	Atenolol	Indomethacin	6.0 (-8.7 to 20.7)
Duration of migraine, years	Atenolol	Induprofen	11.0 (-3.7 to 25.7)
Duration of migraine, years	Atenolol	Magnesium	21.8 (7.1 to 36.6)
Duration of migraine, years	Atenolol	Methysergide	6.0 (-8.7 to 20.7)
Duration of migraine, years	Atenolol	Metoprolol	6.7 (-5.3 to 18.7)
Duration of migraine, years	Atenolol	Naproxen sodium	9.4 (-5.3 to 24.1)
Duration of migraine, years	Atenolol	Nicardipine	18.0 (3.3 to 32.7)
Duration of migraine, years	Atenolol	Nifedipine	17.2 (2.5 to 31.9)
Duration of migraine, years	Atenolol	Nimodipine	7.8 (-5.0 to 20.5)
Duration of migraine, years	Atenolol	Propranolol	9.1 (-2.9 to 21.2)
Duration of migraine, years	Atenolol	Topiramate	16.7 (5.1 to 28.4)
Duration of migraine, years	Atenolol	Valproate	12.0 (-2.7 to 26.7)
Duration of migraine, years	Atenolol	Verapamil	12.6 (-2.1 to 27.3)
Duration of migraine, years	Clonidine	Dihydroergotamine	0.1 (-9.4 to 9.6)
Duration of migraine, years	Clonidine	Divalproex	-6.6 (-16.1 to 2.9)
Duration of migraine, years	Clonidine	Gabapentin	-4.8 (-16.8 to 7.2)
Duration of migraine, years	Clonidine	Indomethacin	-4.0 (-16.0 to 8.0)
Duration of migraine, years	Clonidine	Induprofen	1.0 (-11.0 to 13.0)
Duration of migraine, years	Clonidine	Magnesium	11.8 (-0.2 to 23.9)
Duration of migraine, years	Clonidine	Methysergide	-4.0 (-16.0 to 8.0)
Duration of migraine, years	Clonidine	Metoprolol	-3.3 (-11.8 to 5.2)
Duration of migraine, years	Clonidine	Naproxen sodium	-0.6 (-12.6 to 11.4)
Duration of migraine, years	Clonidine	Nicardipine	8.0 (-4.0 to 20.0)
Duration of migraine, years	Clonidine	Nifedipine	7.2 (-4.8 to 19.2)
Duration of migraine, years	Clonidine	Nimodipine	-2.3 (-11.8 to 7.3)
Duration of migraine, years	Clonidine	Propranolol	-0.9 (-9.4 to 7.6)
Duration of migraine, years	Clonidine	Topiramate	6.7 (-1.3 to 14.7)
Duration of migraine, years	Clonidine	Valproate	2.0 (-10.0 to 14.0)
Duration of migraine, years	Clonidine	Verapamil	2.6 (-9.4 to 14.6)
Duration of migraine, years	Dihydroergotamine	Divalproex	-6.7 (-17.1 to 3.7)
Duration of migraine, years	Dihydroergotamine	Gabapentin	-4.9 (-17.7 to 7.9)
Duration of migraine, years	Dihydroergotamine	Indomethacin	-4.1 (-16.9 to 8.7)
Duration of migraine, years	Dihydroergotamine	Induprofen	0.9 (-11.9 to 13.7)
Duration of migraine, years	Dihydroergotamine	Magnesium	11.7 (-1.0 to 24.5)
Duration of migraine, years	Dihydroergotamine	Methysergide	-4.1 (-16.9 to 8.7)
Duration of migraine, years	Dihydroergotamine	Metoprolol	-3.4 (-12.9 to 6.1)
Duration of migraine, years	Dihydroergotamine	Naproxen sodium	-0.7 (-13.5 to 12.1)
Duration of migraine, years	Dihydroergotamine	Nicardipine	7.9 (-4.9 to 20.7)
Duration of migraine, years	Dihydroergotamine	Nifedipine	7.1 (-5.7 to 19.9)
Duration of migraine, years	Dihydroergotamine	Nimodipine	-2.4 (-12.8 to 8.1)
Duration of migraine, years	Dihydroergotamine	Propranolol	-1.0 (-10.5 to 8.5)
Duration of migraine, years	Dihydroergotamine	Topiramate	6.6 (-2.4 to 15.6)
Duration of migraine, years	Dihydroergotamine	Valproate	1.9 (-10.9 to 14.7)
Duration of migraine, years	Dihydroergotamine	Verapamil	2.5 (-10.3 to 15.3)
Duration of migraine, years	Divalproex	Gabapentin	1.8 (-11.0 to 14.6)
Duration of migraine, years	Divalproex	Indomethacin	2.6 (-10.2 to 15.4)
Duration of migraine, years	Divalproex	Induprofen	7.6 (-5.2 to 20.4)
Duration of migraine, years	Divalproex	Magnesium	18.4 (5.7 to 31.2)
Duration of migraine, years	Divalproex	Methysergide	2.6 (-10.2 to 15.4)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Duration of migraine, years	Divalproex	Metoprolol	3.3 (-6.2 to 12.8)
Duration of migraine, years	Divalproex	Naproxen sodium	6.0 (-6.8 to 18.8)
Duration of migraine, years	Divalproex	Nicardipine	14.6 (1.8 to 27.4)
Duration of migraine, years	Divalproex	Nifedipine	13.8 (1.0 to 26.6)
Duration of migraine, years	Divalproex	Nimodipine	4.4 (-6.1 to 14.8)
Duration of migraine, years	Divalproex	Propranolol	5.7 (-3.8 to 15.2)
Duration of migraine, years	Divalproex	Topiramate	13.3 (4.3 to 22.3)
Duration of migraine, years	Divalproex	Valproate	8.6 (-4.2 to 21.4)
Duration of migraine, years	Divalproex	Verapamil	9.2 (-3.6 to 22.0)
Duration of migraine, years	Gabapentin	Indomethacin	0.8 (-13.9 to 15.5)
Duration of migraine, years	Gabapentin	Induprofen	5.8 (-8.9 to 20.5)
Duration of migraine, years	Gabapentin	Magnesium	16.6 (1.9 to 31.4)
Duration of migraine, years	Gabapentin	Methysergide	0.8 (-13.9 to 15.5)
Duration of migraine, years	Gabapentin	Metoprolol	1.5 (-10.5 to 13.5)
Duration of migraine, years	Gabapentin	Naproxen sodium	4.2 (-10.5 to 18.9)
Duration of migraine, years	Gabapentin	Nicardipine	12.8 (-1.9 to 27.5)
Duration of migraine, years	Gabapentin	Nifedipine	12.0 (-2.7 to 26.7)
Duration of migraine, years	Gabapentin	Nimodipine	2.6 (-10.2 to 15.3)
Duration of migraine, years	Gabapentin	Propranolol	3.9 (-8.1 to 16.0)
Duration of migraine, years	Gabapentin	Topiramate	11.5 (-0.1 to 23.2)
Duration of migraine, years	Gabapentin	Valproate	6.8 (-7.9 to 21.5)
Duration of migraine, years	Gabapentin	Verapamil	7.4 (-7.3 to 22.1)
Duration of migraine, years	Indomethacin	Induprofen	5.0 (-9.7 to 19.7)
Duration of migraine, years	Indomethacin	Magnesium	15.8 (1.1 to 30.6)
Duration of migraine, years	Indomethacin	Methysergide	0.0 (-14.7 to 14.7)
Duration of migraine, years	Indomethacin	Metoprolol	0.7 (-11.3 to 12.7)
Duration of migraine, years	Indomethacin	Naproxen sodium	3.4 (-11.3 to 18.1)
Duration of migraine, years	Indomethacin	Nicardipine	12.0 (-2.7 to 26.7)
Duration of migraine, years	Indomethacin	Nifedipine	11.2 (-3.5 to 25.9)
Duration of migraine, years	Indomethacin	Nimodipine	1.8 (-11.0 to 14.5)
Duration of migraine, years	Indomethacin	Propranolol	3.1 (-8.9 to 15.2)
Duration of migraine, years	Indomethacin	Topiramate	10.7 (-0.9 to 22.4)
Duration of migraine, years	Indomethacin	Valproate	6.0 (-8.7 to 20.7)
Duration of migraine, years	Indomethacin	Verapamil	6.6 (-8.1 to 21.3)
Duration of migraine, years	Induprofen	Magnesium	10.8 (-3.9 to 25.6)
Duration of migraine, years	Induprofen	Methysergide	-5.0 (-19.7 to 9.7)
Duration of migraine, years	Induprofen	Metoprolol	-4.3 (-16.3 to 7.7)
Duration of migraine, years	Induprofen	Naproxen sodium	-1.6 (-16.3 to 13.1)
Duration of migraine, years	Induprofen	Nicardipine	7.0 (-7.7 to 21.7)
Duration of migraine, years	Induprofen	Nifedipine	6.2 (-8.5 to 20.9)
Duration of migraine, years	Induprofen	Nimodipine	-3.3 (-16.0 to 9.5)
Duration of migraine, years	Induprofen	Propranolol	-1.9 (-13.9 to 10.2)
Duration of migraine, years	Induprofen	Topiramate	5.7 (-5.9 to 17.4)
Duration of migraine, years	Induprofen	Valproate	1.0 (-13.7 to 15.7)
Duration of migraine, years	Induprofen	Verapamil	1.6 (-13.1 to 16.3)
Duration of migraine, years	Magnesium	Naproxen sodium	-12.4 (-27.2 to 2.3)
Duration of migraine, years	Magnesium	Nicardipine	-3.8 (-18.6 to 10.9)
Duration of migraine, years	Magnesium	Nifedipine	-4.6 (-19.4 to 10.1)
Duration of migraine, years	Magnesium	Nimodipine	-14.1 (-26.8 to -1.3)
Duration of migraine, years	Magnesium	Propranolol	-12.7 (-24.7 to -0.7)
Duration of migraine, years	Magnesium	Topiramate	-5.1 (-16.8 to 6.5)
Duration of migraine, years	Magnesium	Valproate	-9.8 (-24.6 to 4.9)
Duration of migraine, years	Magnesium	Verapamil	-9.2 (-24.0 to 5.5)
Duration of migraine, years	Methysergide	Magnesium	15.8 (1.1 to 30.6)
Duration of migraine, years	Methysergide	Metoprolol	0.7 (-11.3 to 12.7)
Duration of migraine, years	Methysergide	Naproxen sodium	3.4 (-11.3 to 18.1)
Duration of migraine, years	Methysergide	Nicardipine	12.0 (-2.7 to 26.7)
Duration of migraine, years	Methysergide	Nifedipine	11.2 (-3.5 to 25.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Duration of migraine, years	Methysergide	Nimodipine	1.8 (-11.0 to 14.5)
Duration of migraine, years	Methysergide	Propranolol	3.1 (-8.9 to 15.2)
Duration of migraine, years	Methysergide	Topiramate	10.7 (-0.9 to 22.4)
Duration of migraine, years	Methysergide	Valproate	6.0 (-8.7 to 20.7)
Duration of migraine, years	Methysergide	Verapamil	6.6 (-8.1 to 21.3)
Duration of migraine, years	Metoprolol	Magnesium	15.1 (3.1 to 27.2)
Duration of migraine, years	Metoprolol	Naproxen sodium	2.7 (-9.3 to 14.7)
Duration of migraine, years	Metoprolol	Nicardipine	11.3 (-0.7 to 23.3)
Duration of migraine, years	Metoprolol	Nifedipine	10.5 (-1.5 to 22.5)
Duration of migraine, years	Metoprolol	Nimodipine	1.1 (-8.5 to 10.6)
Duration of migraine, years	Metoprolol	Propranolol	2.4 (-6.1 to 10.9)
Duration of migraine, years	Metoprolol	Topiramate	10.0 (2.0 to 18.0)
Duration of migraine, years	Metoprolol	Valproate	5.3 (-6.7 to 17.3)
Duration of migraine, years	Metoprolol	Verapamil	5.9 (-6.1 to 17.9)
Duration of migraine, years	Naproxen sodium	Nicardipine	8.6 (-6.1 to 23.3)
Duration of migraine, years	Naproxen sodium	Nifedipine	7.8 (-6.9 to 22.5)
Duration of migraine, years	Naproxen sodium	Nimodipine	-1.7 (-14.4 to 11.1)
Duration of migraine, years	Naproxen sodium	Propranolol	-0.3 (-12.3 to 11.8)
Duration of migraine, years	Naproxen sodium	Topiramate	7.3 (-4.3 to 19.0)
Duration of migraine, years	Naproxen sodium	Valproate	2.6 (-12.1 to 17.3)
Duration of migraine, years	Naproxen sodium	Verapamil	3.2 (-11.5 to 17.9)
Duration of migraine, years	Nicardipine	Nifedipine	-0.8 (-15.5 to 13.9)
Duration of migraine, years	Nicardipine	Nimodipine	-10.3 (-23.0 to 2.5)
Duration of migraine, years	Nicardipine	Propranolol	-8.9 (-20.9 to 3.2)
Duration of migraine, years	Nicardipine	Topiramate	-1.3 (-12.9 to 10.4)
Duration of migraine, years	Nicardipine	Valproate	-6.0 (-20.7 to 8.7)
Duration of migraine, years	Nicardipine	Verapamil	-5.4 (-20.1 to 9.3)
Duration of migraine, years	Nifedipine	Nimodipine	-9.5 (-22.2 to 3.3)
Duration of migraine, years	Nifedipine	Propranolol	-8.1 (-20.1 to 4.0)
Duration of migraine, years	Nifedipine	Topiramate	-0.5 (-12.1 to 11.2)
Duration of migraine, years	Nifedipine	Valproate	-5.2 (-19.9 to 9.5)
Duration of migraine, years	Nifedipine	Verapamil	-4.6 (-19.3 to 10.1)
Duration of migraine, years	Nimodipine	Propranolol	1.4 (-8.1 to 10.9)
Duration of migraine, years	Nimodipine	Topiramate	9.0 (-0.1 to 18.0)
Duration of migraine, years	Nimodipine	Valproate	4.3 (-8.5 to 17.0)
Duration of migraine, years	Nimodipine	Verapamil	4.9 (-7.9 to 17.6)
Duration of migraine, years	Propranolol	Topiramate	7.6 (-0.4 to 15.5)
Duration of migraine, years	Propranolol	Valproate	2.9 (-9.2 to 14.9)
Duration of migraine, years	Propranolol	Verapamil	3.5 (-8.6 to 15.5)
Duration of migraine, years	Topiramate	Valproate	-4.7 (-16.4 to 6.9)
Duration of migraine, years	Topiramate	Verapamil	-4.1 (-15.8 to 7.5)
Duration of migraine, years	Valproate	Verapamil	0.6 (-14.1 to 15.3)
Baseline migraine frequency/month	Acebutolol	Acetazolamide	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Acebutolol	Alprenolol	1.8 (-6.6 to 10.2)
Baseline migraine frequency/month	Acebutolol	Atenolol	2.8 (-5.6 to 11.2)
Baseline migraine frequency/month	Acebutolol	Carbamazepine	1.8 (-6.5 to 10.2)
Baseline migraine frequency/month	Acebutolol	Clonidine	0.1 (-6.6 to 6.7)
Baseline migraine frequency/month	Acebutolol	Dihydroergocryptine	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Acebutolol	Dihydroergotamine	0.4 (-6.9 to 7.7)
Baseline migraine frequency/month	Acebutolol	Divalproex	3.3 (-4.0 to 10.6)
Baseline migraine frequency/month	Acebutolol	Femoxetine	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Acebutolol	Fluoxetine	-2.2 (-10.6 to 6.2)
Baseline migraine frequency/month	Acebutolol	Gabapentin	-0.2 (-7.0 to 6.7)
Baseline migraine frequency/month	Acebutolol	Induprofen	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Acebutolol	Ketoprofen	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Acebutolol	Lamotrigine	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Acebutolol	Lisinopril	2.5 (-5.9 to 10.9)
Baseline migraine frequency/month	Acebutolol	Lisuride	1.3 (-7.1 to 9.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Acebutolol	Magnesium	-0.2 (-7.5 to 7.1)
Baseline migraine frequency/month	Acebutolol	Methysergide	1.8 (-6.6 to 10.2)
Baseline migraine frequency/month	Acebutolol	Metoprolol	-0.8 (-7.6 to 6.0)
Baseline migraine frequency/month	Acebutolol	Montelukast	-0.3 (-8.7 to 8.1)
Baseline migraine frequency/month	Acebutolol	Naproxen sodium	3.5 (-4.9 to 11.9)
Baseline migraine frequency/month	Acebutolol	Nicardipine	0.5 (-7.8 to 8.9)
Baseline migraine frequency/month	Acebutolol	Nifedipine	-5.2 (-13.6 to 3.2)
Baseline migraine frequency/month	Acebutolol	Nimodipine	-0.5 (-7.7 to 6.8)
Baseline migraine frequency/month	Acebutolol	Oxcarbazepine	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Acebutolol	Pindolol	2.8 (-5.6 to 11.2)
Baseline migraine frequency/month	Acebutolol	Propranolol	1.6 (-5.1 to 8.2)
Baseline migraine frequency/month	Acebutolol	Rofecoxib	-0.4 (-8.8 to 8.0)
Baseline migraine frequency/month	Acebutolol	Telmisartan	-1.4 (-9.8 to 7.0)
Baseline migraine frequency/month	Acebutolol	Timolol	1.0 (-6.3 to 8.2)
Baseline migraine frequency/month	Acebutolol	Topiramate	-2.3 (-8.5 to 3.9)
Baseline migraine frequency/month	Acebutolol	Valproate	-0.5 (-7.8 to 6.8)
Baseline migraine frequency/month	Acebutolol	Verapamil	-0.5 (-8.9 to 7.9)
Baseline migraine frequency/month	Acebutolol	Vigabatrin	2.8 (-5.6 to 11.2)
Baseline migraine frequency/month	Acetazolamide	Alprenolol	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Acetazolamide	Atenolol	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Acetazolamide	Carbamazepine	2.0 (-6.3 to 10.4)
Baseline migraine frequency/month	Acetazolamide	Clonidine	0.3 (-6.4 to 6.9)
Baseline migraine frequency/month	Acetazolamide	Dihydroergocryptine	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Acetazolamide	Dihydroergotamine	0.6 (-6.7 to 7.9)
Baseline migraine frequency/month	Acetazolamide	Divalproex	3.5 (-3.8 to 10.8)
Baseline migraine frequency/month	Acetazolamide	Femoxetine	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Acetazolamide	Fluoxetine	-2.0 (-10.4 to 6.4)
Baseline migraine frequency/month	Acetazolamide	Gabapentin	0.0 (-6.8 to 6.9)
Baseline migraine frequency/month	Acetazolamide	Induprofen	0.2 (-8.2 to 8.6)
Baseline migraine frequency/month	Acetazolamide	Ketoprofen	2.2 (-6.2 to 10.6)
Baseline migraine frequency/month	Acetazolamide	Lamotrigine	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Acetazolamide	Lisinopril	2.7 (-5.7 to 11.1)
Baseline migraine frequency/month	Acetazolamide	Lisuride	1.5 (-6.9 to 9.9)
Baseline migraine frequency/month	Acetazolamide	Magnesium	0.0 (-7.3 to 7.3)
Baseline migraine frequency/month	Acetazolamide	Methysergide	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Acetazolamide	Metoprolol	-0.6 (-7.4 to 6.2)
Baseline migraine frequency/month	Acetazolamide	Montelukast	-0.1 (-8.5 to 8.3)
Baseline migraine frequency/month	Acetazolamide	Naproxen sodium	3.7 (-4.7 to 12.1)
Baseline migraine frequency/month	Acetazolamide	Nicardipine	0.7 (-7.6 to 9.1)
Baseline migraine frequency/month	Acetazolamide	Nifedipine	-5.0 (-13.4 to 3.4)
Baseline migraine frequency/month	Acetazolamide	Nimodipine	-0.3 (-7.5 to 7.0)
Baseline migraine frequency/month	Acetazolamide	Oxcarbazepine	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Acetazolamide	Pindolol	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Acetazolamide	Propranolol	1.8 (-4.9 to 8.4)
Baseline migraine frequency/month	Acetazolamide	Rofecoxib	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Acetazolamide	Telmisartan	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Acetazolamide	Timolol	1.2 (-6.1 to 8.4)
Baseline migraine frequency/month	Acetazolamide	Topiramate	-2.1 (-8.3 to 4.1)
Baseline migraine frequency/month	Acetazolamide	Valproate	-0.3 (-7.6 to 7.0)
Baseline migraine frequency/month	Acetazolamide	Verapamil	-0.3 (-8.7 to 8.1)
Baseline migraine frequency/month	Acetazolamide	Vigabatrin	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Alprenolol	Atenolol	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Alprenolol	Carbamazepine	0.0 (-8.3 to 8.4)
Baseline migraine frequency/month	Alprenolol	Clonidine	-1.7 (-8.4 to 4.9)
Baseline migraine frequency/month	Alprenolol	Dihydroergocryptine	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Alprenolol	Dihydroergotamine	-1.4 (-8.7 to 5.9)
Baseline migraine frequency/month	Alprenolol	Divalproex	1.5 (-5.8 to 8.8)
Baseline migraine frequency/month	Alprenolol	Femoxetine	-2.0 (-10.4 to 6.4)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Alprenolol	Fluoxetine	-4.0 (-12.4 to 4.4)
Baseline migraine frequency/month	Alprenolol	Gabapentin	-2.0 (-8.8 to 4.9)
Baseline migraine frequency/month	Alprenolol	Induprofen	-1.8 (-10.2 to 6.6)
Baseline migraine frequency/month	Alprenolol	Ketoprofen	0.2 (-8.2 to 8.6)
Baseline migraine frequency/month	Alprenolol	Lamotrigine	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Alprenolol	Lisinopril	0.7 (-7.7 to 9.1)
Baseline migraine frequency/month	Alprenolol	Lisuride	-0.5 (-8.9 to 7.9)
Baseline migraine frequency/month	Alprenolol	Magnesium	-2.0 (-9.3 to 5.3)
Baseline migraine frequency/month	Alprenolol	Methysergide	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Alprenolol	Metoprolol	-2.6 (-9.4 to 4.2)
Baseline migraine frequency/month	Alprenolol	Montelukast	-2.1 (-10.5 to 6.3)
Baseline migraine frequency/month	Alprenolol	Naproxen sodium	1.7 (-6.7 to 10.1)
Baseline migraine frequency/month	Alprenolol	Nicardipine	-1.3 (-9.6 to 7.1)
Baseline migraine frequency/month	Alprenolol	Nifedipine	-7.0 (-15.4 to 1.4)
Baseline migraine frequency/month	Alprenolol	Nimodipine	-2.3 (-9.5 to 5.0)
Baseline migraine frequency/month	Alprenolol	Oxcarbazepine	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Alprenolol	Pindolol	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Alprenolol	Propranolol	-0.3 (-6.9 to 6.4)
Baseline migraine frequency/month	Alprenolol	Rofecoxib	-2.2 (-10.6 to 6.2)
Baseline migraine frequency/month	Alprenolol	Telmisartan	-3.2 (-11.6 to 5.2)
Baseline migraine frequency/month	Alprenolol	Timolol	-0.9 (-8.1 to 6.4)
Baseline migraine frequency/month	Alprenolol	Topiramate	-4.1 (-10.3 to 2.1)
Baseline migraine frequency/month	Alprenolol	Valproate	-2.3 (-9.6 to 5.0)
Baseline migraine frequency/month	Alprenolol	Verapamil	-2.3 (-10.7 to 6.1)
Baseline migraine frequency/month	Alprenolol	Vigabatrin	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Atenolol	Carbamazepine	-1.0 (-9.3 to 7.4)
Baseline migraine frequency/month	Atenolol	Clonidine	-2.7 (-9.4 to 3.9)
Baseline migraine frequency/month	Atenolol	Dihydroergocryptine	-4.0 (-12.4 to 4.4)
Baseline migraine frequency/month	Atenolol	Dihydroergotamine	-2.4 (-9.7 to 4.9)
Baseline migraine frequency/month	Atenolol	Divalproex	0.5 (-6.8 to 7.8)
Baseline migraine frequency/month	Atenolol	Femoxetine	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Atenolol	Fluoxetine	-5.0 (-13.4 to 3.4)
Baseline migraine frequency/month	Atenolol	Gabapentin	-3.0 (-9.8 to 3.9)
Baseline migraine frequency/month	Atenolol	Induprofen	-2.8 (-11.2 to 5.6)
Baseline migraine frequency/month	Atenolol	Ketoprofen	-0.8 (-9.2 to 7.6)
Baseline migraine frequency/month	Atenolol	Lamotrigine	-2.0 (-10.4 to 6.4)
Baseline migraine frequency/month	Atenolol	Lisinopril	-0.3 (-8.7 to 8.1)
Baseline migraine frequency/month	Atenolol	Lisuride	-1.5 (-9.9 to 6.9)
Baseline migraine frequency/month	Atenolol	Magnesium	-3.0 (-10.3 to 4.3)
Baseline migraine frequency/month	Atenolol	Methysergide	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Atenolol	Metoprolol	-3.6 (-10.4 to 3.2)
Baseline migraine frequency/month	Atenolol	Montelukast	-3.1 (-11.5 to 5.3)
Baseline migraine frequency/month	Atenolol	Naproxen sodium	0.7 (-7.7 to 9.1)
Baseline migraine frequency/month	Atenolol	Nicardipine	-2.3 (-10.6 to 6.1)
Baseline migraine frequency/month	Atenolol	Nifedipine	-8.0 (-16.4 to 0.4)
Baseline migraine frequency/month	Atenolol	Nimodipine	-3.3 (-10.5 to 4.0)
Baseline migraine frequency/month	Atenolol	Oxcarbazepine	-4.0 (-12.4 to 4.4)
Baseline migraine frequency/month	Atenolol	Pindolol	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Atenolol	Propranolol	-1.3 (-7.9 to 5.4)
Baseline migraine frequency/month	Atenolol	Rofecoxib	-3.2 (-11.6 to 5.2)
Baseline migraine frequency/month	Atenolol	Telmisartan	-4.2 (-12.6 to 4.2)
Baseline migraine frequency/month	Atenolol	Timolol	-1.9 (-9.1 to 5.4)
Baseline migraine frequency/month	Atenolol	Topiramate	-5.1 (-11.3 to 1.1)
Baseline migraine frequency/month	Atenolol	Valproate	-3.3 (-10.6 to 4.0)
Baseline migraine frequency/month	Atenolol	Verapamil	-3.3 (-11.7 to 5.1)
Baseline migraine frequency/month	Atenolol	Vigabatrin	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Carbamazepine	Clonidine	-1.8 (-8.4 to 4.8)
Baseline migraine frequency/month	Carbamazepine	Dihydroergocryptine	-3.0 (-11.4 to 5.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Carbamazepine	Dihydroergotamine	-1.4 (-8.7 to 5.8)
Baseline migraine frequency/month	Carbamazepine	Divalproex	1.5 (-5.8 to 8.7)
Baseline migraine frequency/month	Carbamazepine	Femoxetine	-2.0 (-10.4 to 6.3)
Baseline migraine frequency/month	Carbamazepine	Fluoxetine	-4.0 (-12.4 to 4.3)
Baseline migraine frequency/month	Carbamazepine	Gabapentin	-2.0 (-8.8 to 4.8)
Baseline migraine frequency/month	Carbamazepine	Induprofen	-1.8 (-10.2 to 6.5)
Baseline migraine frequency/month	Carbamazepine	Ketoprofen	0.2 (-8.2 to 8.5)
Baseline migraine frequency/month	Carbamazepine	Lamotrigine	-1.1 (-9.4 to 7.3)
Baseline migraine frequency/month	Carbamazepine	Lisinopril	0.7 (-7.7 to 9.0)
Baseline migraine frequency/month	Carbamazepine	Lisuride	-0.5 (-8.9 to 7.8)
Baseline migraine frequency/month	Carbamazepine	Magnesium	-2.0 (-9.3 to 5.2)
Baseline migraine frequency/month	Carbamazepine	Methysergide	0.0 (-8.4 to 8.3)
Baseline migraine frequency/month	Carbamazepine	Metoprolol	-2.6 (-9.5 to 4.2)
Baseline migraine frequency/month	Carbamazepine	Montelukast	-2.1 (-10.5 to 6.2)
Baseline migraine frequency/month	Carbamazepine	Naproxen sodium	1.7 (-6.7 to 10.0)
Baseline migraine frequency/month	Carbamazepine	Nicardipine	-1.3 (-9.7 to 7.1)
Baseline migraine frequency/month	Carbamazepine	Nifedipine	-7.0 (-15.4 to 1.3)
Baseline migraine frequency/month	Carbamazepine	Nimodipine	-2.3 (-9.5 to 5.0)
Baseline migraine frequency/month	Carbamazepine	Oxcarbazepine	-3.0 (-11.4 to 5.3)
Baseline migraine frequency/month	Carbamazepine	Pindolol	1.0 (-7.4 to 9.3)
Baseline migraine frequency/month	Carbamazepine	Propranolol	-0.3 (-6.9 to 6.3)
Baseline migraine frequency/month	Carbamazepine	Rofecoxib	-2.3 (-10.6 to 6.1)
Baseline migraine frequency/month	Carbamazepine	Telmisartan	-3.2 (-11.6 to 5.1)
Baseline migraine frequency/month	Carbamazepine	Timolol	-0.9 (-8.1 to 6.4)
Baseline migraine frequency/month	Carbamazepine	Topiramate	-4.2 (-10.4 to 2.1)
Baseline migraine frequency/month	Carbamazepine	Valproate	-2.3 (-9.6 to 4.9)
Baseline migraine frequency/month	Carbamazepine	Verapamil	-2.3 (-10.7 to 6.0)
Baseline migraine frequency/month	Carbamazepine	Vigabatrin	1.0 (-7.4 to 9.3)
Baseline migraine frequency/month	Clonidine	Dihydroergocryptine	-1.3 (-7.9 to 5.4)
Baseline migraine frequency/month	Clonidine	Dihydroergotamine	0.3 (-4.8 to 5.5)
Baseline migraine frequency/month	Clonidine	Divalproex	3.2 (-1.9 to 8.4)
Baseline migraine frequency/month	Clonidine	Femoxetine	-0.3 (-6.9 to 6.4)
Baseline migraine frequency/month	Clonidine	Fluoxetine	-2.3 (-8.9 to 4.4)
Baseline migraine frequency/month	Clonidine	Gabapentin	-0.2 (-4.7 to 4.3)
Baseline migraine frequency/month	Clonidine	Induprofen	-0.1 (-6.7 to 6.6)
Baseline migraine frequency/month	Clonidine	Ketoprofen	1.9 (-4.7 to 8.6)
Baseline migraine frequency/month	Clonidine	Lamotrigine	0.7 (-5.9 to 7.3)
Baseline migraine frequency/month	Clonidine	Lisinopril	2.4 (-4.2 to 9.1)
Baseline migraine frequency/month	Clonidine	Lisuride	1.2 (-5.4 to 7.9)
Baseline migraine frequency/month	Clonidine	Magnesium	-0.3 (-5.4 to 4.9)
Baseline migraine frequency/month	Clonidine	Methysergide	1.7 (-4.9 to 8.4)
Baseline migraine frequency/month	Clonidine	Metoprolol	-0.8 (-5.4 to 3.7)
Baseline migraine frequency/month	Clonidine	Montelukast	-0.4 (-7.0 to 6.3)
Baseline migraine frequency/month	Clonidine	Naproxen sodium	3.4 (-3.2 to 10.1)
Baseline migraine frequency/month	Clonidine	Nicardipine	0.5 (-6.1 to 7.1)
Baseline migraine frequency/month	Clonidine	Nifedipine	-5.3 (-11.9 to 1.4)
Baseline migraine frequency/month	Clonidine	Nimodipine	-0.5 (-5.6 to 4.6)
Baseline migraine frequency/month	Clonidine	Oxcarbazepine	-1.3 (-7.9 to 5.4)
Baseline migraine frequency/month	Clonidine	Pindolol	2.7 (-3.9 to 9.4)
Baseline migraine frequency/month	Clonidine	Propranolol	1.5 (-2.7 to 5.7)
Baseline migraine frequency/month	Clonidine	Rofecoxib	-0.5 (-7.1 to 6.1)
Baseline migraine frequency/month	Clonidine	Telmisartan	-1.5 (-8.1 to 5.2)
Baseline migraine frequency/month	Clonidine	Timolol	0.9 (-4.2 to 6.0)
Baseline migraine frequency/month	Clonidine	Topiramate	-2.4 (-5.9 to 1.1)
Baseline migraine frequency/month	Clonidine	Valproate	-0.6 (-5.7 to 4.6)
Baseline migraine frequency/month	Clonidine	Verapamil	-0.6 (-7.2 to 6.1)
Baseline migraine frequency/month	Clonidine	Vigabatrin	2.7 (-3.9 to 9.4)
Baseline migraine frequency/month	Dihydroergocryptine	Dihydroergotamine	1.6 (-5.7 to 8.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Dihydroergocryptine	Divalproex	4.5 (-2.8 to 11.8)
Baseline migraine frequency/month	Dihydroergocryptine	Femoxetine	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Dihydroergocryptine	Fluoxetine	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Dihydroergocryptine	Gabapentin	1.0 (-5.8 to 7.9)
Baseline migraine frequency/month	Dihydroergocryptine	Induprofen	1.2 (-7.2 to 9.6)
Baseline migraine frequency/month	Dihydroergocryptine	Ketoprofen	3.2 (-5.2 to 11.6)
Baseline migraine frequency/month	Dihydroergocryptine	Lamotrigine	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Dihydroergocryptine	Lisinopril	3.7 (-4.7 to 12.1)
Baseline migraine frequency/month	Dihydroergocryptine	Lisuride	2.5 (-5.9 to 10.9)
Baseline migraine frequency/month	Dihydroergocryptine	Magnesium	1.0 (-6.3 to 8.3)
Baseline migraine frequency/month	Dihydroergocryptine	Methysergide	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Dihydroergocryptine	Metoprolol	0.4 (-6.4 to 7.2)
Baseline migraine frequency/month	Dihydroergocryptine	Montelukast	0.9 (-7.5 to 9.3)
Baseline migraine frequency/month	Dihydroergocryptine	Naproxen sodium	4.7 (-3.7 to 13.1)
Baseline migraine frequency/month	Dihydroergocryptine	Nicardipine	1.7 (-6.6 to 10.1)
Baseline migraine frequency/month	Dihydroergocryptine	Nifedipine	-4.0 (-12.4 to 4.4)
Baseline migraine frequency/month	Dihydroergocryptine	Nimodipine	0.8 (-6.5 to 8.0)
Baseline migraine frequency/month	Dihydroergocryptine	Oxcarbazepine	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Dihydroergocryptine	Pindolol	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Dihydroergocryptine	Propranolol	2.8 (-3.9 to 9.4)
Baseline migraine frequency/month	Dihydroergocryptine	Rofecoxib	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Dihydroergocryptine	Telmisartan	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Dihydroergocryptine	Timolol	2.2 (-5.1 to 9.4)
Baseline migraine frequency/month	Dihydroergocryptine	Topiramate	-1.1 (-7.3 to 5.1)
Baseline migraine frequency/month	Dihydroergocryptine	Valproate	0.7 (-6.6 to 8.0)
Baseline migraine frequency/month	Dihydroergocryptine	Verapamil	0.7 (-7.7 to 9.1)
Baseline migraine frequency/month	Dihydroergocryptine	Vigabatrin	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Dihydroergotamine	Divalproex	2.9 (-3.0 to 8.8)
Baseline migraine frequency/month	Dihydroergotamine	Femoxetine	-0.6 (-7.9 to 6.7)
Baseline migraine frequency/month	Dihydroergotamine	Fluoxetine	-2.6 (-9.9 to 4.7)
Baseline migraine frequency/month	Dihydroergotamine	Gabapentin	-0.6 (-6.0 to 4.8)
Baseline migraine frequency/month	Dihydroergotamine	Induprofen	-0.4 (-7.7 to 6.9)
Baseline migraine frequency/month	Dihydroergotamine	Ketoprofen	1.6 (-5.7 to 8.9)
Baseline migraine frequency/month	Dihydroergotamine	Lamotrigine	0.4 (-6.9 to 7.6)
Baseline migraine frequency/month	Dihydroergotamine	Lisinopril	2.1 (-5.2 to 9.4)
Baseline migraine frequency/month	Dihydroergotamine	Lisuride	0.9 (-6.4 to 8.2)
Baseline migraine frequency/month	Dihydroergotamine	Magnesium	-0.6 (-6.5 to 5.3)
Baseline migraine frequency/month	Dihydroergotamine	Methysergide	1.4 (-5.9 to 8.7)
Baseline migraine frequency/month	Dihydroergotamine	Metoprolol	-1.2 (-6.6 to 4.2)
Baseline migraine frequency/month	Dihydroergotamine	Montelukast	-0.7 (-8.0 to 6.6)
Baseline migraine frequency/month	Dihydroergotamine	Naproxen sodium	3.1 (-4.2 to 10.4)
Baseline migraine frequency/month	Dihydroergotamine	Nicardipine	0.1 (-7.1 to 7.4)
Baseline migraine frequency/month	Dihydroergotamine	Nifedipine	-5.6 (-12.9 to 1.7)
Baseline migraine frequency/month	Dihydroergotamine	Nimodipine	-0.9 (-6.8 to 5.1)
Baseline migraine frequency/month	Dihydroergotamine	Oxcarbazepine	-1.6 (-8.9 to 5.7)
Baseline migraine frequency/month	Dihydroergotamine	Pindolol	2.4 (-4.9 to 9.7)
Baseline migraine frequency/month	Dihydroergotamine	Propranolol	1.2 (-4.0 to 6.3)
Baseline migraine frequency/month	Dihydroergotamine	Rofecoxib	-0.8 (-8.1 to 6.4)
Baseline migraine frequency/month	Dihydroergotamine	Telmisartan	-1.8 (-9.1 to 5.5)
Baseline migraine frequency/month	Dihydroergotamine	Timolol	0.6 (-5.4 to 6.5)
Baseline migraine frequency/month	Dihydroergotamine	Topiramate	-2.7 (-7.3 to 1.9)
Baseline migraine frequency/month	Dihydroergotamine	Valproate	-0.9 (-6.8 to 5.0)
Baseline migraine frequency/month	Dihydroergotamine	Verapamil	-0.9 (-8.2 to 6.4)
Baseline migraine frequency/month	Dihydroergotamine	Vigabatrin	2.4 (-4.9 to 9.7)
Baseline migraine frequency/month	Divalproex	Femoxetine	-3.5 (-10.8 to 3.8)
Baseline migraine frequency/month	Divalproex	Fluoxetine	-5.5 (-12.8 to 1.8)
Baseline migraine frequency/month	Divalproex	Gabapentin	-3.5 (-8.9 to 1.9)
Baseline migraine frequency/month	Divalproex	Induprofen	-3.3 (-10.6 to 4.0)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Divalproex	Ketoprofen	-1.3 (-8.6 to 6.0)
Baseline migraine frequency/month	Divalproex	Lamotrigine	-2.5 (-9.8 to 4.7)
Baseline migraine frequency/month	Divalproex	Lisinopril	-0.8 (-8.1 to 6.5)
Baseline migraine frequency/month	Divalproex	Lisuride	-2.0 (-9.3 to 5.3)
Baseline migraine frequency/month	Divalproex	Magnesium	-3.5 (-9.4 to 2.4)
Baseline migraine frequency/month	Divalproex	Methysergide	-1.5 (-8.8 to 5.8)
Baseline migraine frequency/month	Divalproex	Metoprolol	-4.1 (-9.5 to 1.3)
Baseline migraine frequency/month	Divalproex	Montelukast	-3.6 (-10.9 to 3.7)
Baseline migraine frequency/month	Divalproex	Naproxen sodium	0.2 (-7.1 to 7.5)
Baseline migraine frequency/month	Divalproex	Nicardipine	-2.8 (-10.0 to 4.5)
Baseline migraine frequency/month	Divalproex	Nifedipine	-8.5 (-15.8 to -1.2)
Baseline migraine frequency/month	Divalproex	Nimodipine	-3.8 (-9.7 to 2.2)
Baseline migraine frequency/month	Divalproex	Oxcarbazepine	-4.5 (-11.8 to 2.8)
Baseline migraine frequency/month	Divalproex	Pindolol	-0.5 (-7.8 to 6.8)
Baseline migraine frequency/month	Divalproex	Propranolol	-1.8 (-6.9 to 3.4)
Baseline migraine frequency/month	Divalproex	Rofecoxib	-3.7 (-11.0 to 3.5)
Baseline migraine frequency/month	Divalproex	Telmisartan	-4.7 (-12.0 to 2.6)
Baseline migraine frequency/month	Divalproex	Timolol	-2.4 (-8.3 to 3.6)
Baseline migraine frequency/month	Divalproex	Topiramate	-5.6 (-10.2 to -1.0)
Baseline migraine frequency/month	Divalproex	Valproate	-3.8 (-9.7 to 2.1)
Baseline migraine frequency/month	Divalproex	Verapamil	-3.8 (-11.1 to 3.5)
Baseline migraine frequency/month	Divalproex	Vigabatrin	-0.5 (-7.8 to 6.8)
Baseline migraine frequency/month	Femoxetine	Fluoxetine	-2.0 (-10.4 to 6.4)
Baseline migraine frequency/month	Femoxetine	Gabapentin	0.0 (-6.8 to 6.9)
Baseline migraine frequency/month	Femoxetine	Induprofen	0.2 (-8.2 to 8.6)
Baseline migraine frequency/month	Femoxetine	Ketoprofen	2.2 (-6.2 to 10.6)
Baseline migraine frequency/month	Femoxetine	Lamotrigine	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Femoxetine	Lisinopril	2.7 (-5.7 to 11.1)
Baseline migraine frequency/month	Femoxetine	Lisuride	1.5 (-6.9 to 9.9)
Baseline migraine frequency/month	Femoxetine	Magnesium	0.0 (-7.3 to 7.3)
Baseline migraine frequency/month	Femoxetine	Methysergide	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Femoxetine	Metoprolol	-0.6 (-7.4 to 6.2)
Baseline migraine frequency/month	Femoxetine	Montelukast	-0.1 (-8.5 to 8.3)
Baseline migraine frequency/month	Femoxetine	Naproxen sodium	3.7 (-4.7 to 12.1)
Baseline migraine frequency/month	Femoxetine	Nicardipine	0.7 (-7.6 to 9.1)
Baseline migraine frequency/month	Femoxetine	Nifedipine	-5.0 (-13.4 to 3.4)
Baseline migraine frequency/month	Femoxetine	Nimodipine	-0.3 (-7.5 to 7.0)
Baseline migraine frequency/month	Femoxetine	Oxcarbazepine	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Femoxetine	Pindolol	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Femoxetine	Propranolol	1.8 (-4.9 to 8.4)
Baseline migraine frequency/month	Femoxetine	Rofecoxib	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Femoxetine	Telmisartan	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Femoxetine	Timolol	1.2 (-6.1 to 8.4)
Baseline migraine frequency/month	Femoxetine	Topiramate	-2.1 (-8.3 to 4.1)
Baseline migraine frequency/month	Femoxetine	Valproate	-0.3 (-7.6 to 7.0)
Baseline migraine frequency/month	Femoxetine	Verapamil	-0.3 (-8.7 to 8.1)
Baseline migraine frequency/month	Femoxetine	Vigabatrin	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Fluoxetine	Gabapentin	2.0 (-4.8 to 8.9)
Baseline migraine frequency/month	Fluoxetine	Induprofen	2.2 (-6.2 to 10.6)
Baseline migraine frequency/month	Fluoxetine	Ketoprofen	4.2 (-4.2 to 12.6)
Baseline migraine frequency/month	Fluoxetine	Lamotrigine	3.0 (-5.4 to 11.4)
Baseline migraine frequency/month	Fluoxetine	Lisinopril	4.7 (-3.7 to 13.1)
Baseline migraine frequency/month	Fluoxetine	Lisuride	3.5 (-4.9 to 11.9)
Baseline migraine frequency/month	Fluoxetine	Magnesium	2.0 (-5.3 to 9.3)
Baseline migraine frequency/month	Fluoxetine	Methysergide	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Fluoxetine	Metoprolol	1.4 (-5.4 to 8.2)
Baseline migraine frequency/month	Fluoxetine	Montelukast	1.9 (-6.5 to 10.3)
Baseline migraine frequency/month	Fluoxetine	Naproxen sodium	5.7 (-2.7 to 14.1)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Fluoxetine	Nicardipine	2.7 (-5.6 to 11.1)
Baseline migraine frequency/month	Fluoxetine	Nifedipine	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Fluoxetine	Nimodipine	1.8 (-5.5 to 9.0)
Baseline migraine frequency/month	Fluoxetine	Oxcarbazepine	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Fluoxetine	Pindolol	5.0 (-3.4 to 13.4)
Baseline migraine frequency/month	Fluoxetine	Propranolol	3.8 (-2.9 to 10.4)
Baseline migraine frequency/month	Fluoxetine	Rofecoxib	1.8 (-6.6 to 10.2)
Baseline migraine frequency/month	Fluoxetine	Telmisartan	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Fluoxetine	Timolol	3.2 (-4.1 to 10.4)
Baseline migraine frequency/month	Fluoxetine	Topiramate	-0.1 (-6.3 to 6.1)
Baseline migraine frequency/month	Fluoxetine	Valproate	1.7 (-5.6 to 9.0)
Baseline migraine frequency/month	Fluoxetine	Verapamil	1.7 (-6.7 to 10.1)
Baseline migraine frequency/month	Fluoxetine	Vigabatrin	5.0 (-3.4 to 13.4)
Baseline migraine frequency/month	Gabapentin	Induprofen	0.2 (-6.7 to 7.0)
Baseline migraine frequency/month	Gabapentin	Ketoprofen	2.2 (-4.7 to 9.0)
Baseline migraine frequency/month	Gabapentin	Lamotrigine	0.9 (-5.9 to 7.8)
Baseline migraine frequency/month	Gabapentin	Lisinopril	2.7 (-4.2 to 9.5)
Baseline migraine frequency/month	Gabapentin	Lisuride	1.5 (-5.4 to 8.3)
Baseline migraine frequency/month	Gabapentin	Magnesium	0.0 (-5.4 to 5.4)
Baseline migraine frequency/month	Gabapentin	Methysergide	2.0 (-4.9 to 8.8)
Baseline migraine frequency/month	Gabapentin	Metoprolol	-0.6 (-5.5 to 4.2)
Baseline migraine frequency/month	Gabapentin	Montelukast	-0.1 (-7.0 to 6.7)
Baseline migraine frequency/month	Gabapentin	Naproxen sodium	3.7 (-3.2 to 10.5)
Baseline migraine frequency/month	Gabapentin	Nicardipine	0.7 (-6.1 to 7.5)
Baseline migraine frequency/month	Gabapentin	Nifedipine	-5.0 (-11.9 to 1.8)
Baseline migraine frequency/month	Gabapentin	Nimodipine	-0.3 (-5.7 to 5.1)
Baseline migraine frequency/month	Gabapentin	Oxcarbazepine	-1.0 (-7.9 to 5.8)
Baseline migraine frequency/month	Gabapentin	Pindolol	3.0 (-3.9 to 9.8)
Baseline migraine frequency/month	Gabapentin	Propranolol	1.7 (-2.8 to 6.2)
Baseline migraine frequency/month	Gabapentin	Rofecoxib	-0.3 (-7.1 to 6.6)
Baseline migraine frequency/month	Gabapentin	Telmisartan	-1.2 (-8.1 to 5.6)
Baseline migraine frequency/month	Gabapentin	Timolol	1.1 (-4.3 to 6.5)
Baseline migraine frequency/month	Gabapentin	Topiramate	-2.2 (-6.1 to 1.7)
Baseline migraine frequency/month	Gabapentin	Valproate	-0.3 (-5.7 to 5.1)
Baseline migraine frequency/month	Gabapentin	Verapamil	-0.3 (-7.2 to 6.5)
Baseline migraine frequency/month	Gabapentin	Vigabatrin	3.0 (-3.9 to 9.8)
Baseline migraine frequency/month	Induprofen	Ketoprofen	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Induprofen	Lamotrigine	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Induprofen	Lisinopril	2.5 (-5.9 to 10.9)
Baseline migraine frequency/month	Induprofen	Lisuride	1.3 (-7.1 to 9.7)
Baseline migraine frequency/month	Induprofen	Magnesium	-0.2 (-7.5 to 7.1)
Baseline migraine frequency/month	Induprofen	Methysergide	1.8 (-6.6 to 10.2)
Baseline migraine frequency/month	Induprofen	Metoprolol	-0.8 (-7.6 to 6.0)
Baseline migraine frequency/month	Induprofen	Montelukast	-0.3 (-8.7 to 8.1)
Baseline migraine frequency/month	Induprofen	Naproxen sodium	3.5 (-4.9 to 11.9)
Baseline migraine frequency/month	Induprofen	Nicardipine	0.5 (-7.8 to 8.9)
Baseline migraine frequency/month	Induprofen	Nifedipine	-5.2 (-13.6 to 3.2)
Baseline migraine frequency/month	Induprofen	Nimodipine	-0.5 (-7.7 to 6.8)
Baseline migraine frequency/month	Induprofen	Oxcarbazepine	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Induprofen	Pindolol	2.8 (-5.6 to 11.2)
Baseline migraine frequency/month	Induprofen	Propranolol	1.6 (-5.1 to 8.2)
Baseline migraine frequency/month	Induprofen	Rofecoxib	-0.4 (-8.8 to 8.0)
Baseline migraine frequency/month	Induprofen	Telmisartan	-1.4 (-9.8 to 7.0)
Baseline migraine frequency/month	Induprofen	Timolol	1.0 (-6.3 to 8.2)
Baseline migraine frequency/month	Induprofen	Topiramate	-2.3 (-8.5 to 3.9)
Baseline migraine frequency/month	Induprofen	Valproate	-0.5 (-7.8 to 6.8)
Baseline migraine frequency/month	Induprofen	Verapamil	-0.5 (-8.9 to 7.9)
Baseline migraine frequency/month	Induprofen	Vigabatrin	2.8 (-5.6 to 11.2)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Ketoprofen	Lamotrigine	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Ketoprofen	Lisinopril	0.5 (-7.9 to 8.9)
Baseline migraine frequency/month	Ketoprofen	Lisuride	-0.7 (-9.1 to 7.7)
Baseline migraine frequency/month	Ketoprofen	Magnesium	-2.2 (-9.5 to 5.1)
Baseline migraine frequency/month	Ketoprofen	Methysergide	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Ketoprofen	Metoprolol	-2.8 (-9.6 to 4.0)
Baseline migraine frequency/month	Ketoprofen	Montelukast	-2.3 (-10.7 to 6.1)
Baseline migraine frequency/month	Ketoprofen	Naproxen sodium	1.5 (-6.9 to 9.9)
Baseline migraine frequency/month	Ketoprofen	Nicardipine	-1.5 (-9.8 to 6.9)
Baseline migraine frequency/month	Ketoprofen	Nifedipine	-7.2 (-15.6 to 1.2)
Baseline migraine frequency/month	Ketoprofen	Nimodipine	-2.5 (-9.7 to 4.8)
Baseline migraine frequency/month	Ketoprofen	Oxcarbazepine	-3.2 (-11.6 to 5.2)
Baseline migraine frequency/month	Ketoprofen	Pindolol	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Ketoprofen	Propranolol	-0.5 (-7.1 to 6.2)
Baseline migraine frequency/month	Ketoprofen	Rofecoxib	-2.4 (-10.8 to 6.0)
Baseline migraine frequency/month	Ketoprofen	Telmisartan	-3.4 (-11.8 to 5.0)
Baseline migraine frequency/month	Ketoprofen	Timolol	-1.1 (-8.3 to 6.2)
Baseline migraine frequency/month	Ketoprofen	Topiramate	-4.3 (-10.5 to 1.9)
Baseline migraine frequency/month	Ketoprofen	Valproate	-2.5 (-9.8 to 4.8)
Baseline migraine frequency/month	Ketoprofen	Verapamil	-2.5 (-10.9 to 5.9)
Baseline migraine frequency/month	Ketoprofen	Vigabatrin	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Lamotrigine	Lisinopril	1.7 (-6.7 to 10.1)
Baseline migraine frequency/month	Lamotrigine	Lisuride	0.5 (-7.9 to 8.9)
Baseline migraine frequency/month	Lamotrigine	Magnesium	-1.0 (-8.2 to 6.3)
Baseline migraine frequency/month	Lamotrigine	Methysergide	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Lamotrigine	Metoprolol	-1.6 (-8.4 to 5.3)
Baseline migraine frequency/month	Lamotrigine	Montelukast	-1.1 (-9.5 to 7.3)
Baseline migraine frequency/month	Lamotrigine	Naproxen sodium	2.7 (-5.7 to 11.1)
Baseline migraine frequency/month	Lamotrigine	Nicardipine	-0.2 (-8.6 to 8.1)
Baseline migraine frequency/month	Lamotrigine	Nifedipine	-6.0 (-14.4 to 2.4)
Baseline migraine frequency/month	Lamotrigine	Nimodipine	-1.2 (-8.5 to 6.0)
Baseline migraine frequency/month	Lamotrigine	Oxcarbazepine	-2.0 (-10.4 to 6.4)
Baseline migraine frequency/month	Lamotrigine	Pindolol	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Lamotrigine	Propranolol	0.8 (-5.9 to 7.4)
Baseline migraine frequency/month	Lamotrigine	Rofecoxib	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Lamotrigine	Telmisartan	-2.2 (-10.6 to 6.2)
Baseline migraine frequency/month	Lamotrigine	Timolol	0.2 (-7.1 to 7.4)
Baseline migraine frequency/month	Lamotrigine	Topiramate	-3.1 (-9.3 to 3.1)
Baseline migraine frequency/month	Lamotrigine	Valproate	-1.3 (-8.5 to 6.0)
Baseline migraine frequency/month	Lamotrigine	Verapamil	-1.3 (-9.7 to 7.1)
Baseline migraine frequency/month	Lamotrigine	Vigabatrin	2.0 (-6.4 to 10.4)
Baseline migraine frequency/month	Lisinopril	Lisuride	-1.2 (-9.6 to 7.2)
Baseline migraine frequency/month	Lisinopril	Magnesium	-2.7 (-10.0 to 4.6)
Baseline migraine frequency/month	Lisinopril	Methysergide	-0.7 (-9.1 to 7.7)
Baseline migraine frequency/month	Lisinopril	Metoprolol	-3.3 (-10.1 to 3.5)
Baseline migraine frequency/month	Lisinopril	Montelukast	-2.8 (-11.2 to 5.6)
Baseline migraine frequency/month	Lisinopril	Naproxen sodium	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Lisinopril	Nicardipine	-2.0 (-10.3 to 6.4)
Baseline migraine frequency/month	Lisinopril	Nifedipine	-7.7 (-16.1 to 0.7)
Baseline migraine frequency/month	Lisinopril	Nimodipine	-3.0 (-10.2 to 4.3)
Baseline migraine frequency/month	Lisinopril	Oxcarbazepine	-3.7 (-12.1 to 4.7)
Baseline migraine frequency/month	Lisinopril	Pindolol	0.3 (-8.1 to 8.7)
Baseline migraine frequency/month	Lisinopril	Propranolol	-1.0 (-7.6 to 5.7)
Baseline migraine frequency/month	Lisinopril	Rofecoxib	-2.9 (-11.3 to 5.5)
Baseline migraine frequency/month	Lisinopril	Telmisartan	-3.9 (-12.3 to 4.5)
Baseline migraine frequency/month	Lisinopril	Timolol	-1.6 (-8.8 to 5.7)
Baseline migraine frequency/month	Lisinopril	Topiramate	-4.8 (-11.0 to 1.4)
Baseline migraine frequency/month	Lisinopril	Valproate	-3.0 (-10.3 to 4.3)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Lisinopril	Verapamil	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Lisinopril	Vigabatrin	0.3 (-8.1 to 8.7)
Baseline migraine frequency/month	Lisuride	Magnesium	-1.5 (-8.8 to 5.8)
Baseline migraine frequency/month	Lisuride	Methysergide	0.5 (-7.9 to 8.9)
Baseline migraine frequency/month	Lisuride	Metoprolol	-2.1 (-8.9 to 4.7)
Baseline migraine frequency/month	Lisuride	Montelukast	-1.6 (-10.0 to 6.8)
Baseline migraine frequency/month	Lisuride	Naproxen sodium	2.2 (-6.2 to 10.6)
Baseline migraine frequency/month	Lisuride	Nicardipine	-0.8 (-9.1 to 7.6)
Baseline migraine frequency/month	Lisuride	Nifedipine	-6.5 (-14.9 to 1.9)
Baseline migraine frequency/month	Lisuride	Nimodipine	-1.8 (-9.0 to 5.5)
Baseline migraine frequency/month	Lisuride	Oxcarbazepine	-2.5 (-10.9 to 5.9)
Baseline migraine frequency/month	Lisuride	Pindolol	1.5 (-6.9 to 9.9)
Baseline migraine frequency/month	Lisuride	Propranolol	0.3 (-6.4 to 6.9)
Baseline migraine frequency/month	Lisuride	Rofecoxib	-1.7 (-10.1 to 6.7)
Baseline migraine frequency/month	Lisuride	Telmisartan	-2.7 (-11.1 to 5.7)
Baseline migraine frequency/month	Lisuride	Timolol	-0.4 (-7.6 to 6.9)
Baseline migraine frequency/month	Lisuride	Topiramate	-3.6 (-9.8 to 2.6)
Baseline migraine frequency/month	Lisuride	Valproate	-1.8 (-9.1 to 5.5)
Baseline migraine frequency/month	Lisuride	Verapamil	-1.8 (-10.2 to 6.6)
Baseline migraine frequency/month	Lisuride	Vigabatrin	1.5 (-6.9 to 9.9)
Baseline migraine frequency/month	Magnesium	Montelukast	-0.1 (-7.4 to 7.2)
Baseline migraine frequency/month	Magnesium	Naproxen sodium	3.7 (-3.6 to 11.0)
Baseline migraine frequency/month	Magnesium	Nicardipine	0.7 (-6.5 to 8.0)
Baseline migraine frequency/month	Magnesium	Nifedipine	-5.0 (-12.3 to 2.3)
Baseline migraine frequency/month	Magnesium	Nimodipine	-0.3 (-6.2 to 5.7)
Baseline migraine frequency/month	Magnesium	Oxcarbazepine	-1.0 (-8.3 to 6.3)
Baseline migraine frequency/month	Magnesium	Pindolol	3.0 (-4.3 to 10.3)
Baseline migraine frequency/month	Magnesium	Propranolol	1.8 (-3.4 to 6.9)
Baseline migraine frequency/month	Magnesium	Rofecoxib	-0.2 (-7.5 to 7.0)
Baseline migraine frequency/month	Magnesium	Telmisartan	-1.2 (-8.5 to 6.1)
Baseline migraine frequency/month	Magnesium	Timolol	1.2 (-4.8 to 7.1)
Baseline migraine frequency/month	Magnesium	Topiramate	-2.1 (-6.7 to 2.5)
Baseline migraine frequency/month	Magnesium	Valproate	-0.3 (-6.2 to 5.6)
Baseline migraine frequency/month	Magnesium	Verapamil	-0.3 (-7.6 to 7.0)
Baseline migraine frequency/month	Magnesium	Vigabatrin	3.0 (-4.3 to 10.3)
Baseline migraine frequency/month	Methysergide	Magnesium	-2.0 (-9.3 to 5.3)
Baseline migraine frequency/month	Methysergide	Metoprolol	-2.6 (-9.4 to 4.2)
Baseline migraine frequency/month	Methysergide	Montelukast	-2.1 (-10.5 to 6.3)
Baseline migraine frequency/month	Methysergide	Naproxen sodium	1.7 (-6.7 to 10.1)
Baseline migraine frequency/month	Methysergide	Nicardipine	-1.3 (-9.6 to 7.1)
Baseline migraine frequency/month	Methysergide	Nifedipine	-7.0 (-15.4 to 1.4)
Baseline migraine frequency/month	Methysergide	Nimodipine	-2.3 (-9.5 to 5.0)
Baseline migraine frequency/month	Methysergide	Oxcarbazepine	-3.0 (-11.4 to 5.4)
Baseline migraine frequency/month	Methysergide	Pindolol	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Methysergide	Propranolol	-0.3 (-6.9 to 6.4)
Baseline migraine frequency/month	Methysergide	Rofecoxib	-2.2 (-10.6 to 6.2)
Baseline migraine frequency/month	Methysergide	Telmisartan	-3.2 (-11.6 to 5.2)
Baseline migraine frequency/month	Methysergide	Timolol	-0.9 (-8.1 to 6.4)
Baseline migraine frequency/month	Methysergide	Topiramate	-4.1 (-10.3 to 2.1)
Baseline migraine frequency/month	Methysergide	Valproate	-2.3 (-9.6 to 5.0)
Baseline migraine frequency/month	Methysergide	Verapamil	-2.3 (-10.7 to 6.1)
Baseline migraine frequency/month	Methysergide	Vigabatrin	1.0 (-7.4 to 9.4)
Baseline migraine frequency/month	Metoprolol	Magnesium	0.6 (-4.8 to 6.0)
Baseline migraine frequency/month	Metoprolol	Montelukast	0.5 (-6.3 to 7.3)
Baseline migraine frequency/month	Metoprolol	Naproxen sodium	4.3 (-2.5 to 11.1)
Baseline migraine frequency/month	Metoprolol	Nicardipine	1.3 (-5.5 to 8.2)
Baseline migraine frequency/month	Metoprolol	Nifedipine	-4.4 (-11.2 to 2.4)
Baseline migraine frequency/month	Metoprolol	Nimodipine	0.3 (-5.1 to 5.8)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Metoprolol	Oxcarbazepine	-0.4 (-7.2 to 6.4)
Baseline migraine frequency/month	Metoprolol	Pindolol	3.6 (-3.2 to 10.4)
Baseline migraine frequency/month	Metoprolol	Propranolol	2.3 (-2.2 to 6.9)
Baseline migraine frequency/month	Metoprolol	Rofecoxib	0.4 (-6.5 to 7.2)
Baseline migraine frequency/month	Metoprolol	Telmisartan	-0.6 (-7.4 to 6.2)
Baseline migraine frequency/month	Metoprolol	Timolol	1.7 (-3.7 to 7.2)
Baseline migraine frequency/month	Metoprolol	Topiramate	-1.5 (-5.4 to 2.4)
Baseline migraine frequency/month	Metoprolol	Valproate	0.3 (-5.1 to 5.7)
Baseline migraine frequency/month	Metoprolol	Verapamil	0.3 (-6.5 to 7.1)
Baseline migraine frequency/month	Metoprolol	Vigabatrin	3.6 (-3.2 to 10.4)
Baseline migraine frequency/month	Montelukast	Naproxen sodium	3.8 (-4.6 to 12.2)
Baseline migraine frequency/month	Montelukast	Nicardipine	0.8 (-7.5 to 9.2)
Baseline migraine frequency/month	Montelukast	Nifedipine	-4.9 (-13.3 to 3.5)
Baseline migraine frequency/month	Montelukast	Nimodipine	-0.2 (-7.4 to 7.1)
Baseline migraine frequency/month	Montelukast	Oxcarbazepine	-0.9 (-9.3 to 7.5)
Baseline migraine frequency/month	Montelukast	Pindolol	3.1 (-5.3 to 11.5)
Baseline migraine frequency/month	Montelukast	Propranolol	1.9 (-4.8 to 8.5)
Baseline migraine frequency/month	Montelukast	Rofecoxib	-0.1 (-8.5 to 8.3)
Baseline migraine frequency/month	Montelukast	Telmisartan	-1.1 (-9.5 to 7.3)
Baseline migraine frequency/month	Montelukast	Timolol	1.3 (-6.0 to 8.5)
Baseline migraine frequency/month	Montelukast	Topiramate	-2.0 (-8.2 to 4.2)
Baseline migraine frequency/month	Montelukast	Valproate	-0.2 (-7.5 to 7.1)
Baseline migraine frequency/month	Montelukast	Verapamil	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Montelukast	Vigabatrin	3.1 (-5.3 to 11.5)
Baseline migraine frequency/month	Naproxen sodium	Nicardipine	-3.0 (-11.3 to 5.4)
Baseline migraine frequency/month	Naproxen sodium	Nifedipine	-8.7 (-17.1 to -0.3)
Baseline migraine frequency/month	Naproxen sodium	Nimodipine	-4.0 (-11.2 to 3.3)
Baseline migraine frequency/month	Naproxen sodium	Oxcarbazepine	-4.7 (-13.1 to 3.7)
Baseline migraine frequency/month	Naproxen sodium	Pindolol	-0.7 (-9.1 to 7.7)
Baseline migraine frequency/month	Naproxen sodium	Propranolol	-2.0 (-8.6 to 4.7)
Baseline migraine frequency/month	Naproxen sodium	Rofecoxib	-3.9 (-12.3 to 4.5)
Baseline migraine frequency/month	Naproxen sodium	Telmisartan	-4.9 (-13.3 to 3.5)
Baseline migraine frequency/month	Naproxen sodium	Timolol	-2.6 (-9.8 to 4.7)
Baseline migraine frequency/month	Naproxen sodium	Topiramate	-5.8 (-12.0 to 0.4)
Baseline migraine frequency/month	Naproxen sodium	Valproate	-4.0 (-11.3 to 3.3)
Baseline migraine frequency/month	Naproxen sodium	Verapamil	-4.0 (-12.4 to 4.4)
Baseline migraine frequency/month	Naproxen sodium	Vigabatrin	-0.7 (-9.1 to 7.7)
Baseline migraine frequency/month	Nicardipine	Nifedipine	-5.7 (-14.1 to 2.6)
Baseline migraine frequency/month	Nicardipine	Nimodipine	-1.0 (-8.2 to 6.3)
Baseline migraine frequency/month	Nicardipine	Oxcarbazepine	-1.7 (-10.1 to 6.6)
Baseline migraine frequency/month	Nicardipine	Pindolol	2.3 (-6.1 to 10.6)
Baseline migraine frequency/month	Nicardipine	Propranolol	1.0 (-5.6 to 7.6)
Baseline migraine frequency/month	Nicardipine	Rofecoxib	-1.0 (-9.3 to 7.4)
Baseline migraine frequency/month	Nicardipine	Telmisartan	-1.9 (-10.3 to 6.4)
Baseline migraine frequency/month	Nicardipine	Timolol	0.4 (-6.8 to 7.7)
Baseline migraine frequency/month	Nicardipine	Topiramate	-2.9 (-9.1 to 3.4)
Baseline migraine frequency/month	Nicardipine	Valproate	-1.0 (-8.3 to 6.2)
Baseline migraine frequency/month	Nicardipine	Verapamil	-1.0 (-9.4 to 7.3)
Baseline migraine frequency/month	Nicardipine	Vigabatrin	2.3 (-6.1 to 10.6)
Baseline migraine frequency/month	Nifedipine	Nimodipine	4.8 (-2.5 to 12.0)
Baseline migraine frequency/month	Nifedipine	Oxcarbazepine	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Nifedipine	Pindolol	8.0 (-0.4 to 16.4)
Baseline migraine frequency/month	Nifedipine	Propranolol	6.8 (0.1 to 13.4)
Baseline migraine frequency/month	Nifedipine	Rofecoxib	4.8 (-3.6 to 13.2)
Baseline migraine frequency/month	Nifedipine	Telmisartan	3.8 (-4.6 to 12.2)
Baseline migraine frequency/month	Nifedipine	Timolol	6.2 (-1.1 to 13.4)
Baseline migraine frequency/month	Nifedipine	Topiramate	2.9 (-3.3 to 9.1)
Baseline migraine frequency/month	Nifedipine	Valproate	4.7 (-2.6 to 12.0)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

Baseline migraine frequency/month	Nifedipine	Verapamil	4.7 (-3.7 to 13.1)
Baseline migraine frequency/month	Nifedipine	Vigabatrin	8.0 (-0.4 to 16.4)
Baseline migraine frequency/month	Nimodipine	Oxcarbazepine	-0.8 (-8.0 to 6.5)
Baseline migraine frequency/month	Nimodipine	Pindolol	3.3 (-4.0 to 10.5)
Baseline migraine frequency/month	Nimodipine	Propranolol	2.0 (-3.1 to 7.1)
Baseline migraine frequency/month	Nimodipine	Rofecoxib	0.0 (-7.2 to 7.3)
Baseline migraine frequency/month	Nimodipine	Telmisartan	-1.0 (-8.2 to 6.3)
Baseline migraine frequency/month	Nimodipine	Timolol	1.4 (-4.5 to 7.3)
Baseline migraine frequency/month	Nimodipine	Topiramate	-1.9 (-6.5 to 2.7)
Baseline migraine frequency/month	Nimodipine	Valproate	-0.1 (-6.0 to 5.9)
Baseline migraine frequency/month	Nimodipine	Verapamil	-0.1 (-7.3 to 7.2)
Baseline migraine frequency/month	Nimodipine	Vigabatrin	3.3 (-4.0 to 10.5)
Baseline migraine frequency/month	Oxcarbazepine	Pindolol	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Oxcarbazepine	Propranolol	2.8 (-3.9 to 9.4)
Baseline migraine frequency/month	Oxcarbazepine	Rofecoxib	0.8 (-7.6 to 9.2)
Baseline migraine frequency/month	Oxcarbazepine	Telmisartan	-0.2 (-8.6 to 8.2)
Baseline migraine frequency/month	Oxcarbazepine	Timolol	2.2 (-5.1 to 9.4)
Baseline migraine frequency/month	Oxcarbazepine	Topiramate	-1.1 (-7.3 to 5.1)
Baseline migraine frequency/month	Oxcarbazepine	Valproate	0.7 (-6.6 to 8.0)
Baseline migraine frequency/month	Oxcarbazepine	Verapamil	0.7 (-7.7 to 9.1)
Baseline migraine frequency/month	Oxcarbazepine	Vigabatrin	4.0 (-4.4 to 12.4)
Baseline migraine frequency/month	Pindolol	Propranolol	-1.3 (-7.9 to 5.4)
Baseline migraine frequency/month	Pindolol	Rofecoxib	-3.2 (-11.6 to 5.2)
Baseline migraine frequency/month	Pindolol	Telmisartan	-4.2 (-12.6 to 4.2)
Baseline migraine frequency/month	Pindolol	Timolol	-1.9 (-9.1 to 5.4)
Baseline migraine frequency/month	Pindolol	Topiramate	-5.1 (-11.3 to 1.1)
Baseline migraine frequency/month	Pindolol	Valproate	-3.3 (-10.6 to 4.0)
Baseline migraine frequency/month	Pindolol	Verapamil	-3.3 (-11.7 to 5.1)
Baseline migraine frequency/month	Pindolol	Vigabatrin	0.0 (-8.4 to 8.4)
Baseline migraine frequency/month	Propranolol	Rofecoxib	-2.0 (-8.6 to 4.7)
Baseline migraine frequency/month	Propranolol	Telmisartan	-3.0 (-9.6 to 3.7)
Baseline migraine frequency/month	Propranolol	Timolol	-0.6 (-5.7 to 4.5)
Baseline migraine frequency/month	Propranolol	Topiramate	-3.9 (-7.4 to -0.4)
Baseline migraine frequency/month	Propranolol	Valproate	-2.1 (-7.2 to 3.1)
Baseline migraine frequency/month	Propranolol	Verapamil	-2.1 (-8.7 to 4.6)
Baseline migraine frequency/month	Propranolol	Vigabatrin	1.3 (-5.4 to 7.9)
Baseline migraine frequency/month	Rofecoxib	Telmisartan	-1.0 (-9.4 to 7.4)
Baseline migraine frequency/month	Rofecoxib	Timolol	1.4 (-5.9 to 8.6)
Baseline migraine frequency/month	Rofecoxib	Topiramate	-1.9 (-8.1 to 4.3)
Baseline migraine frequency/month	Rofecoxib	Valproate	-0.1 (-7.3 to 7.2)
Baseline migraine frequency/month	Rofecoxib	Verapamil	-0.1 (-8.5 to 8.3)
Baseline migraine frequency/month	Rofecoxib	Vigabatrin	3.2 (-5.2 to 11.6)
Baseline migraine frequency/month	Telmisartan	Timolol	2.4 (-4.9 to 9.6)
Baseline migraine frequency/month	Telmisartan	Topiramate	-0.9 (-7.1 to 5.3)
Baseline migraine frequency/month	Telmisartan	Valproate	0.9 (-6.4 to 8.2)
Baseline migraine frequency/month	Telmisartan	Verapamil	0.9 (-7.5 to 9.3)
Baseline migraine frequency/month	Telmisartan	Vigabatrin	4.2 (-4.2 to 12.6)
Baseline migraine frequency/month	Timolol	Topiramate	-3.3 (-7.9 to 1.3)
Baseline migraine frequency/month	Timolol	Valproate	-1.5 (-7.4 to 4.5)
Baseline migraine frequency/month	Timolol	Verapamil	-1.5 (-8.7 to 5.8)
Baseline migraine frequency/month	Timolol	Vigabatrin	1.9 (-5.4 to 9.1)
Baseline migraine frequency/month	Topiramate	Valproate	1.8 (-2.8 to 6.4)
Baseline migraine frequency/month	Topiramate	Verapamil	1.8 (-4.4 to 8.0)
Baseline migraine frequency/month	Topiramate	Vigabatrin	5.1 (-1.1 to 11.3)
Baseline migraine frequency/month	Valproate	Verapamil	0.0 (-7.3 to 7.3)
Baseline migraine frequency/month	Valproate	Vigabatrin	3.3 (-4.0 to 10.6)
Baseline migraine frequency/month	Verapamil	Vigabatrin	3.3 (-5.1 to 11.7)
% naïve	Dihydroergotamine	Femoxetine	-36.7 (-83.9 to 10.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% naïve	Dihydroergotamine	Metoprolol	-17.7 (-53.0 to 17.5)
% naïve	Dihydroergotamine	Pindolol	63.3 (16.1 to 110.6)
% naïve	Dihydroergotamine	Propranolol	37.6 (-9.6 to 84.9)
% naïve	Dihydroergotamine	Timolol	27.6 (-19.6 to 74.9)
% naïve	Dihydroergotamine	Tonabersat	-36.7 (-83.9 to 10.6)
% naïve	Dihydroergotamine	Topiramate	63.3 (16.1 to 110.6)
% naïve	Femoxetine	Metoprolol	18.9 (-25.6 to 63.5)
% naïve	Femoxetine	Pindolol	100.0 (45.4 to 154.6)
% naïve	Femoxetine	Propranolol	74.3 (19.7 to 128.9)
% naïve	Femoxetine	Timolol	64.3 (9.7 to 118.9)
% naïve	Femoxetine	Tonabersat	0.0 (-54.6 to 54.6)
% naïve	Femoxetine	Topiramate	100.0 (45.4 to 154.6)
% naïve	Metoprolol	Pindolol	81.1 (36.5 to 125.6)
% naïve	Metoprolol	Propranolol	55.4 (10.8 to 99.9)
% naïve	Metoprolol	Timolol	45.4 (0.8 to 89.9)
% naïve	Metoprolol	Tonabersat	-18.9 (-63.5 to 25.6)
% naïve	Metoprolol	Topiramate	81.1 (36.5 to 125.6)
% naïve	Pindolol	Propranolol	-25.7 (-80.3 to 28.9)
% naïve	Pindolol	Timolol	-35.7 (-90.3 to 18.9)
% naïve	Pindolol	Tonabersat	-100.0 (-154.6 to -45.4)
% naïve	Pindolol	Topiramate	0.0 (-54.6 to 54.6)
% naïve	Propranolol	Timolol	-10.0 (-64.6 to 44.6)
% naïve	Propranolol	Tonabersat	-74.3 (-128.9 to -19.7)
% naïve	Propranolol	Topiramate	25.7 (-28.9 to 80.3)
% naïve	Timolol	Tonabersat	-64.3 (-118.9 to -9.7)
% naïve	Timolol	Topiramate	35.7 (-18.9 to 90.3)
% naïve	Tonabersat	Topiramate	100.0 (45.4 to 154.6)
% with aura	Acetazolamide	Alprenolol	-8.8 (-112.2 to 94.6)
% with aura	Acetazolamide	Atenolol	9.4 (-80.1 to 98.9)
% with aura	Acetazolamide	Dihydroergocryptine	9.4 (-94.0 to 112.8)
% with aura	Acetazolamide	Dihydroergotamine	-11.6 (-96.1 to 72.8)
% with aura	Acetazolamide	Divalproex	5.4 (-84.1 to 94.9)
% with aura	Acetazolamide	Fluoxetine	-13.2 (-102.7 to 76.3)
% with aura	Acetazolamide	Gabapentin	-37.1 (-126.6 to 52.5)
% with aura	Acetazolamide	Indobufen	9.4 (-94.0 to 112.8)
% with aura	Acetazolamide	Lamotrigine	-30.9 (-134.3 to 72.5)
% with aura	Acetazolamide	Magnesium	-40.6 (-130.1 to 48.9)
% with aura	Acetazolamide	Metoprolol	-40.6 (-130.1 to 48.9)
% with aura	Acetazolamide	Nadolol	-75.0 (-178.4 to 28.4)
% with aura	Acetazolamide	Nicardipine	-90.6 (-194.0 to 12.8)
% with aura	Acetazolamide	Nimodipine	-17.8 (-107.3 to 71.7)
% with aura	Acetazolamide	Pindolol	-40.6 (-144.0 to 62.8)
% with aura	Acetazolamide	Propranolol	-45.9 (-123.4 to 31.7)
% with aura	Acetazolamide	Timolol	-0.1 (-89.6 to 89.4)
% with aura	Acetazolamide	Topiramate	-13.1 (-94.9 to 68.6)
% with aura	Acetazolamide	Valproate	-33.8 (-123.3 to 55.8)
% with aura	Acetazolamide	Verapamil	-32.3 (-135.7 to 71.1)
% with aura	Acetazolamide	Vigabatrin	-34.1 (-137.5 to 69.3)
% with aura	Alprenolol	Atenolol	18.2 (-71.4 to 107.7)
% with aura	Alprenolol	Dihydroergocryptine	18.2 (-85.2 to 121.6)
% with aura	Alprenolol	Dihydroergotamine	-2.9 (-87.3 to 81.6)
% with aura	Alprenolol	Divalproex	14.2 (-75.4 to 103.7)
% with aura	Alprenolol	Fluoxetine	-4.4 (-94.0 to 85.1)
% with aura	Alprenolol	Gabapentin	-28.3 (-117.8 to 61.3)
% with aura	Alprenolol	Indobufen	18.2 (-85.2 to 121.6)
% with aura	Alprenolol	Lamotrigine	-22.1 (-125.5 to 81.3)
% with aura	Alprenolol	Magnesium	-31.8 (-121.4 to 57.7)
% with aura	Alprenolol	Metoprolol	-31.8 (-121.4 to 57.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% with aura	Alprenolol	Nadolol	-66.2 (-169.6 to 37.2)
% with aura	Alprenolol	Nicardipine	-81.8 (-185.2 to 21.6)
% with aura	Alprenolol	Nimodipine	-9.0 (-98.6 to 80.5)
% with aura	Alprenolol	Pindolol	-31.8 (-135.2 to 71.6)
% with aura	Alprenolol	Propranolol	-37.1 (-114.6 to 40.5)
% with aura	Alprenolol	Timolol	8.7 (-80.9 to 98.2)
% with aura	Alprenolol	Topiramate	-4.3 (-86.1 to 77.4)
% with aura	Alprenolol	Valproate	-25.0 (-114.5 to 64.6)
% with aura	Alprenolol	Verapamil	-23.5 (-126.9 to 79.9)
% with aura	Alprenolol	Vigabatrin	-25.3 (-128.7 to 78.1)
% with aura	Atenolol	Dihydroergocryptine	0.0 (-89.5 to 89.5)
% with aura	Atenolol	Dihydroergotamine	-21.0 (-87.8 to 45.7)
% with aura	Atenolol	Divalproex	-4.0 (-77.1 to 69.1)
% with aura	Atenolol	Fluoxetine	-22.6 (-95.7 to 50.5)
% with aura	Atenolol	Gabapentin	-46.5 (-119.6 to 26.7)
% with aura	Atenolol	Indobufen	0.0 (-89.5 to 89.5)
% with aura	Atenolol	Lamotrigine	-40.3 (-129.8 to 49.2)
% with aura	Atenolol	Magnesium	-50.0 (-123.1 to 23.1)
% with aura	Atenolol	Metoprolol	-50.0 (-123.1 to 23.1)
% with aura	Atenolol	Nadolol	-84.4 (-173.9 to 5.1)
% with aura	Atenolol	Nicardipine	-100.0 (-189.5 to -10.5)
% with aura	Atenolol	Nimodipine	-27.2 (-100.3 to 45.9)
% with aura	Atenolol	Pindolol	-50.0 (-139.5 to 39.5)
% with aura	Atenolol	Propranolol	-55.3 (-113.1 to 2.5)
% with aura	Atenolol	Timolol	-9.5 (-82.6 to 63.6)
% with aura	Atenolol	Topiramate	-22.5 (-85.8 to 40.8)
% with aura	Atenolol	Valproate	-43.2 (-116.3 to 30.0)
% with aura	Atenolol	Verapamil	-41.7 (-131.2 to 47.8)
% with aura	Atenolol	Vigabatrin	-43.5 (-133.0 to 46.0)
% with aura	Dihydroergocryptine	Dihydroergotamine	-21.0 (-105.5 to 63.4)
% with aura	Dihydroergocryptine	Divalproex	-4.0 (-93.5 to 85.5)
% with aura	Dihydroergocryptine	Fluoxetine	-22.6 (-112.1 to 66.9)
% with aura	Dihydroergocryptine	Gabapentin	-46.5 (-136.0 to 43.1)
% with aura	Dihydroergocryptine	Indobufen	0.0 (-103.4 to 103.4)
% with aura	Dihydroergocryptine	Lamotrigine	-40.3 (-143.7 to 63.1)
% with aura	Dihydroergocryptine	Magnesium	-50.0 (-139.5 to 39.5)
% with aura	Dihydroergocryptine	Metoprolol	-50.0 (-139.5 to 39.5)
% with aura	Dihydroergocryptine	Nadolol	-84.4 (-187.8 to 19.0)
% with aura	Dihydroergocryptine	Nicardipine	-100.0 (-203.4 to 3.4)
% with aura	Dihydroergocryptine	Nimodipine	-27.2 (-116.7 to 62.3)
% with aura	Dihydroergocryptine	Pindolol	-50.0 (-153.4 to 53.4)
% with aura	Dihydroergocryptine	Propranolol	-55.3 (-132.8 to 22.3)
% with aura	Dihydroergocryptine	Timolol	-9.5 (-99.0 to 80.0)
% with aura	Dihydroergocryptine	Topiramate	-22.5 (-104.3 to 59.2)
% with aura	Dihydroergocryptine	Valproate	-43.2 (-132.7 to 46.4)
% with aura	Dihydroergocryptine	Verapamil	-41.7 (-145.1 to 61.7)
% with aura	Dihydroergocryptine	Vigabatrin	-43.5 (-146.9 to 59.9)
% with aura	Dihydroergotamine	Divalproex	17.0 (-49.7 to 83.8)
% with aura	Dihydroergotamine	Fluoxetine	-1.6 (-68.3 to 65.2)
% with aura	Dihydroergotamine	Gabapentin	-25.4 (-92.2 to 41.3)
% with aura	Dihydroergotamine	Indobufen	21.0 (-63.4 to 105.5)
% with aura	Dihydroergotamine	Lamotrigine	-19.3 (-103.7 to 65.2)
% with aura	Dihydroergotamine	Magnesium	-29.0 (-95.7 to 37.8)
% with aura	Dihydroergotamine	Metoprolol	-29.0 (-95.7 to 37.8)
% with aura	Dihydroergotamine	Nadolol	-63.4 (-147.8 to 21.1)
% with aura	Dihydroergotamine	Nicardipine	-79.0 (-163.4 to 5.5)
% with aura	Dihydroergotamine	Nimodipine	-6.2 (-72.9 to 60.6)
% with aura	Dihydroergotamine	Pindolol	-29.0 (-113.4 to 55.5)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% with aura	Dihydroergotamine	Propranolol	-34.2 (-83.7 to 15.3)
% with aura	Dihydroergotamine	Timolol	11.5 (-55.2 to 78.3)
% with aura	Dihydroergotamine	Topiramate	-1.5 (-57.3 to 54.3)
% with aura	Dihydroergotamine	Valproate	-22.1 (-88.9 to 44.6)
% with aura	Dihydroergotamine	Verapamil	-20.7 (-105.1 to 63.8)
% with aura	Dihydroergotamine	Vigabatrin	-22.5 (-106.9 to 62.0)
% with aura	Divalproex	Fluoxetine	-18.6 (-91.7 to 54.5)
% with aura	Divalproex	Gabapentin	-42.5 (-115.6 to 30.7)
% with aura	Divalproex	Indobufen	4.0 (-85.5 to 93.5)
% with aura	Divalproex	Lamotrigine	-36.3 (-125.8 to 53.2)
% with aura	Divalproex	Magnesium	-46.0 (-119.1 to 27.1)
% with aura	Divalproex	Metoprolol	-46.0 (-119.1 to 27.1)
% with aura	Divalproex	Nadolol	-80.4 (-169.9 to 9.1)
% with aura	Divalproex	Nicardipine	-96.0 (-185.5 to -6.5)
% with aura	Divalproex	Nimodipine	-23.2 (-96.3 to 49.9)
% with aura	Divalproex	Pindolol	-46.0 (-135.5 to 43.5)
% with aura	Divalproex	Propranolol	-51.3 (-109.1 to 6.5)
% with aura	Divalproex	Timolol	-5.5 (-78.6 to 67.6)
% with aura	Divalproex	Topiramate	-18.5 (-81.8 to 44.8)
% with aura	Divalproex	Valproate	-39.2 (-112.3 to 34.0)
% with aura	Divalproex	Verapamil	-37.7 (-127.2 to 51.8)
% with aura	Divalproex	Vigabatrin	-39.5 (-129.0 to 50.0)
% with aura	Fluoxetine	Gabapentin	-23.9 (-97.0 to 49.3)
% with aura	Fluoxetine	Indobufen	22.6 (-66.9 to 112.1)
% with aura	Fluoxetine	Lamotrigine	-17.7 (-107.2 to 71.8)
% with aura	Fluoxetine	Magnesium	-27.4 (-100.5 to 45.7)
% with aura	Fluoxetine	Metoprolol	-27.4 (-100.5 to 45.7)
% with aura	Fluoxetine	Nadolol	-61.8 (-151.3 to 27.7)
% with aura	Fluoxetine	Nicardipine	-77.4 (-166.9 to 12.1)
% with aura	Fluoxetine	Nimodipine	-4.6 (-77.7 to 68.5)
% with aura	Fluoxetine	Pindolol	-27.4 (-116.9 to 62.1)
% with aura	Fluoxetine	Propranolol	-32.7 (-90.5 to 25.1)
% with aura	Fluoxetine	Timolol	13.1 (-60.0 to 86.2)
% with aura	Fluoxetine	Topiramate	0.1 (-63.2 to 63.4)
% with aura	Fluoxetine	Valproate	-20.6 (-93.7 to 52.6)
% with aura	Fluoxetine	Verapamil	-19.1 (-108.6 to 70.4)
% with aura	Fluoxetine	Vigabatrin	-20.9 (-110.4 to 68.6)
% with aura	Gabapentin	Indobufen	46.5 (-43.1 to 136.0)
% with aura	Gabapentin	Lamotrigine	6.2 (-83.4 to 95.7)
% with aura	Gabapentin	Magnesium	-3.6 (-76.7 to 69.6)
% with aura	Gabapentin	Metoprolol	-3.6 (-76.7 to 69.6)
% with aura	Gabapentin	Nadolol	-38.0 (-127.5 to 51.6)
% with aura	Gabapentin	Nicardipine	-53.6 (-143.1 to 36.0)
% with aura	Gabapentin	Nimodipine	19.3 (-53.9 to 92.4)
% with aura	Gabapentin	Pindolol	-3.6 (-93.1 to 86.0)
% with aura	Gabapentin	Propranolol	-8.8 (-66.6 to 49.0)
% with aura	Gabapentin	Timolol	37.0 (-36.2 to 110.1)
% with aura	Gabapentin	Topiramate	23.9 (-39.4 to 87.2)
% with aura	Gabapentin	Valproate	3.3 (-69.8 to 76.4)
% with aura	Gabapentin	Verapamil	4.8 (-84.8 to 94.3)
% with aura	Gabapentin	Vigabatrin	3.0 (-86.6 to 92.5)
% with aura	Indobufen	Lamotrigine	-40.3 (-143.7 to 63.1)
% with aura	Indobufen	Magnesium	-50.0 (-139.5 to 39.5)
% with aura	Indobufen	Metoprolol	-50.0 (-139.5 to 39.5)
% with aura	Indobufen	Nadolol	-84.4 (-187.8 to 19.0)
% with aura	Indobufen	Nicardipine	-100.0 (-203.4 to 3.4)
% with aura	Indobufen	Nimodipine	-27.2 (-116.7 to 62.3)
% with aura	Indobufen	Pindolol	-50.0 (-153.4 to 53.4)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% with aura	Indobufen	Propranolol	-55.3 (-132.8 to 22.3)
% with aura	Indobufen	Timolol	-9.5 (-99.0 to 80.0)
% with aura	Indobufen	Topiramate	-22.5 (-104.3 to 59.2)
% with aura	Indobufen	Valproate	-43.2 (-132.7 to 46.4)
% with aura	Indobufen	Verapamil	-41.7 (-145.1 to 61.7)
% with aura	Indobufen	Vigabatrin	-43.5 (-146.9 to 59.9)
% with aura	Lamotrigine	Magnesium	-9.7 (-99.2 to 79.8)
% with aura	Lamotrigine	Metoprolol	-9.7 (-99.2 to 79.8)
% with aura	Lamotrigine	Nadolol	-44.1 (-147.5 to 59.3)
% with aura	Lamotrigine	Nicardipine	-59.7 (-163.1 to 43.7)
% with aura	Lamotrigine	Nimodipine	13.1 (-76.4 to 102.6)
% with aura	Lamotrigine	Pindolol	-9.7 (-113.1 to 93.7)
% with aura	Lamotrigine	Propranolol	-15.0 (-92.5 to 62.6)
% with aura	Lamotrigine	Timolol	30.8 (-58.7 to 120.3)
% with aura	Lamotrigine	Topiramate	17.8 (-64.0 to 99.5)
% with aura	Lamotrigine	Valproate	-2.9 (-92.4 to 86.7)
% with aura	Lamotrigine	Verapamil	-1.4 (-104.8 to 102.0)
% with aura	Lamotrigine	Vigabatrin	-3.2 (-106.6 to 100.2)
% with aura	Magnesium	Nadolol	-34.4 (-123.9 to 55.1)
% with aura	Magnesium	Nicardipine	-50.0 (-139.5 to 39.5)
% with aura	Magnesium	Nimodipine	22.8 (-50.3 to 95.9)
% with aura	Magnesium	Pindolol	0.0 (-89.5 to 89.5)
% with aura	Magnesium	Propranolol	-5.3 (-63.1 to 52.5)
% with aura	Magnesium	Timolol	40.5 (-32.6 to 113.6)
% with aura	Magnesium	Topiramate	27.5 (-35.8 to 90.8)
% with aura	Magnesium	Valproate	6.9 (-66.3 to 80.0)
% with aura	Magnesium	Verapamil	8.3 (-81.2 to 97.8)
% with aura	Magnesium	Vigabatrin	6.5 (-83.0 to 96.0)
% with aura	Metoprolol	Magnesium	0.0 (-73.1 to 73.1)
% with aura	Metoprolol	Nadolol	-34.4 (-123.9 to 55.1)
% with aura	Metoprolol	Nicardipine	-50.0 (-139.5 to 39.5)
% with aura	Metoprolol	Nimodipine	22.8 (-50.3 to 95.9)
% with aura	Metoprolol	Pindolol	0.0 (-89.5 to 89.5)
% with aura	Metoprolol	Propranolol	-5.3 (-63.1 to 52.5)
% with aura	Metoprolol	Timolol	40.5 (-32.6 to 113.6)
% with aura	Metoprolol	Topiramate	27.5 (-35.8 to 90.8)
% with aura	Metoprolol	Valproate	6.9 (-66.3 to 80.0)
% with aura	Metoprolol	Verapamil	8.3 (-81.2 to 97.8)
% with aura	Metoprolol	Vigabatrin	6.5 (-83.0 to 96.0)
% with aura	Nadolol	Nicardipine	-15.6 (-119.0 to 87.8)
% with aura	Nadolol	Nimodipine	57.2 (-32.3 to 146.7)
% with aura	Nadolol	Pindolol	34.4 (-69.0 to 137.8)
% with aura	Nadolol	Propranolol	29.1 (-48.4 to 106.7)
% with aura	Nadolol	Timolol	74.9 (-14.6 to 164.4)
% with aura	Nadolol	Topiramate	61.9 (-19.9 to 143.6)
% with aura	Nadolol	Valproate	41.3 (-48.3 to 130.8)
% with aura	Nadolol	Verapamil	42.7 (-60.7 to 146.1)
% with aura	Nadolol	Vigabatrin	40.9 (-62.5 to 144.3)
% with aura	Nicardipine	Nimodipine	72.8 (-16.7 to 162.3)
% with aura	Nicardipine	Pindolol	50.0 (-53.4 to 153.4)
% with aura	Nicardipine	Propranolol	44.7 (-32.8 to 122.3)
% with aura	Nicardipine	Timolol	90.5 (1.0 to 180.0)
% with aura	Nicardipine	Topiramate	77.5 (-4.3 to 159.2)
% with aura	Nicardipine	Valproate	56.9 (-32.7 to 146.4)
% with aura	Nicardipine	Verapamil	58.3 (-45.1 to 161.7)
% with aura	Nicardipine	Vigabatrin	56.5 (-46.9 to 159.9)
% with aura	Nimodipine	Pindolol	-22.8 (-112.3 to 66.7)
% with aura	Nimodipine	Propranolol	-28.1 (-85.9 to 29.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% with aura	Nimodipine	Timolol	17.7 (-55.4 to 90.8)
% with aura	Nimodipine	Topiramate	4.7 (-58.6 to 68.0)
% with aura	Nimodipine	Valproate	-16.0 (-89.1 to 57.2)
% with aura	Nimodipine	Verapamil	-14.5 (-104.0 to 75.0)
% with aura	Nimodipine	Vigabatrin	-16.3 (-105.8 to 73.2)
% with aura	Pindolol	Propranolol	-5.3 (-82.8 to 72.3)
% with aura	Pindolol	Timolol	40.5 (-49.0 to 130.0)
% with aura	Pindolol	Topiramate	27.5 (-54.3 to 109.2)
% with aura	Pindolol	Valproate	6.9 (-82.7 to 96.4)
% with aura	Pindolol	Verapamil	8.3 (-95.1 to 111.7)
% with aura	Pindolol	Vigabatrin	6.5 (-96.9 to 109.9)
% with aura	Propranolol	Timolol	45.8 (-12.0 to 103.6)
% with aura	Propranolol	Topiramate	32.7 (-12.0 to 77.5)
% with aura	Propranolol	Valproate	12.1 (-45.7 to 69.9)
% with aura	Propranolol	Verapamil	13.6 (-64.0 to 91.1)
% with aura	Propranolol	Vigabatrin	11.8 (-65.8 to 89.3)
% with aura	Timolol	Topiramate	-13.0 (-76.3 to 50.3)
% with aura	Timolol	Valproate	-33.7 (-106.8 to 39.5)
% with aura	Timolol	Verapamil	-32.2 (-121.7 to 57.3)
% with aura	Timolol	Vigabatrin	-34.0 (-123.5 to 55.5)
% with aura	Topiramate	Valproate	-20.6 (-83.9 to 42.7)
% with aura	Topiramate	Verapamil	-19.2 (-100.9 to 62.6)
% with aura	Topiramate	Vigabatrin	-21.0 (-102.7 to 60.8)
% with aura	Valproate	Verapamil	1.5 (-88.1 to 91.0)
% with aura	Valproate	Vigabatrin	-0.4 (-89.9 to 89.2)
% with aura	Verapamil	Vigabatrin	-1.8 (-105.2 to 101.6)
% loss to followup	Acetazolamide	Amitriptyline	-31.3 (-63.9 to 1.4)
% loss to followup	Acetazolamide	Candesartan	-5.0 (-42.7 to 32.7)
% loss to followup	Acetazolamide	Carbamazepine	-6.3 (-44.0 to 31.4)
% loss to followup	Acetazolamide	Clonidine	-22.5 (-50.5 to 5.4)
% loss to followup	Acetazolamide	Dihydroergotamine	-0.4 (-31.1 to 30.4)
% loss to followup	Acetazolamide	Divalproex	-1.8 (-34.5 to 30.8)
% loss to followup	Acetazolamide	Femoxetine	-24.1 (-53.9 to 5.7)
% loss to followup	Acetazolamide	Fluoxetine	-22.2 (-51.9 to 7.6)
% loss to followup	Acetazolamide	Gabapentin	-2.0 (-32.8 to 28.7)
% loss to followup	Acetazolamide	Guanfacine	-8.0 (-45.7 to 29.7)
% loss to followup	Acetazolamide	Lamotrigine	0.0 (-37.7 to 37.7)
% loss to followup	Acetazolamide	Lisinopril	-22.0 (-59.7 to 15.7)
% loss to followup	Acetazolamide	Lisuride	0.0 (-37.7 to 37.7)
% loss to followup	Acetazolamide	Magnesium	-23.0 (-53.8 to 7.8)
% loss to followup	Acetazolamide	Methysergide	-32.4 (-70.1 to 5.3)
% loss to followup	Acetazolamide	Mianserin	-10.5 (-48.2 to 27.2)
% loss to followup	Acetazolamide	Montelukast	-2.2 (-39.9 to 35.5)
% loss to followup	Acetazolamide	Naproxen sodium	-15.0 (-52.7 to 22.7)
% loss to followup	Acetazolamide	Nicardipine	-14.0 (-51.7 to 23.7)
% loss to followup	Acetazolamide	Nifedipine	-22.0 (-59.7 to 15.7)
% loss to followup	Acetazolamide	Nimodipine	-17.7 (-47.5 to 12.1)
% loss to followup	Acetazolamide	Oxcarbazepine	-3.5 (-41.2 to 34.2)
% loss to followup	Acetazolamide	Propranolol	-14.4 (-42.5 to 13.6)
% loss to followup	Acetazolamide	Telmisartan	-17.0 (-54.7 to 20.7)
% loss to followup	Acetazolamide	Tonabersat	-5.1 (-42.8 to 32.6)
% loss to followup	Acetazolamide	Valproate	-3.5 (-36.1 to 29.1)
% loss to followup	Acetazolamide	Verapamil	-34.0 (-66.6 to -1.4)
% loss to followup	Acetazolamide	Vigabatrin	0.0 (-37.7 to 37.7)
% loss to followup	Amitriptyline	Candesartan	26.3 (-6.4 to 58.9)
% loss to followup	Amitriptyline	Carbamazepine	25.0 (-7.7 to 57.6)
% loss to followup	Amitriptyline	Clonidine	8.7 (-11.9 to 29.4)
% loss to followup	Amitriptyline	Dihydroergotamine	30.9 (6.6 to 55.2)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Amitriptyline	Divalproex	29.4 (2.8 to 56.1)
% loss to followup	Amitriptyline	Femoxetine	7.1 (-15.9 to 30.2)
% loss to followup	Amitriptyline	Fluoxetine	9.1 (-14.0 to 32.2)
% loss to followup	Amitriptyline	Gabapentin	29.2 (4.9 to 53.5)
% loss to followup	Amitriptyline	Guanfacine	23.3 (-9.4 to 55.9)
% loss to followup	Amitriptyline	Lamotrigine	31.3 (-1.4 to 63.9)
% loss to followup	Amitriptyline	Lisinopril	9.3 (-23.4 to 41.9)
% loss to followup	Amitriptyline	Lisuride	31.3 (-1.4 to 63.9)
% loss to followup	Amitriptyline	Magnesium	8.3 (-16.1 to 32.6)
% loss to followup	Amitriptyline	Methysergide	-1.2 (-33.8 to 31.5)
% loss to followup	Amitriptyline	Mianserin	20.8 (-11.9 to 53.4)
% loss to followup	Amitriptyline	Montelukast	29.1 (-3.6 to 61.7)
% loss to followup	Amitriptyline	Naproxen sodium	16.3 (-16.4 to 48.9)
% loss to followup	Amitriptyline	Nicardipine	17.3 (-15.4 to 49.9)
% loss to followup	Amitriptyline	Nifedipine	9.3 (-23.4 to 41.9)
% loss to followup	Amitriptyline	Nimodipine	13.6 (-9.5 to 36.6)
% loss to followup	Amitriptyline	Oxcarbazepine	27.8 (-4.9 to 60.4)
% loss to followup	Amitriptyline	Propranolol	16.8 (-4.0 to 37.6)
% loss to followup	Amitriptyline	Telmisartan	14.3 (-18.4 to 46.9)
% loss to followup	Amitriptyline	Tonabersat	26.2 (-6.5 to 58.8)
% loss to followup	Amitriptyline	Valproate	27.8 (1.1 to 54.4)
% loss to followup	Amitriptyline	Verapamil	-2.8 (-29.4 to 23.9)
% loss to followup	Amitriptyline	Vigabatrin	31.3 (-1.4 to 63.9)
% loss to followup	Candesartan	Carbamazepine	-1.3 (-39.0 to 36.4)
% loss to followup	Candesartan	Clonidine	-17.5 (-45.5 to 10.4)
% loss to followup	Candesartan	Dihydroergotamine	4.6 (-26.1 to 35.4)
% loss to followup	Candesartan	Divalproex	3.2 (-29.5 to 35.8)
% loss to followup	Candesartan	Femoxetine	-19.1 (-48.9 to 10.7)
% loss to followup	Candesartan	Fluoxetine	-17.2 (-46.9 to 12.6)
% loss to followup	Candesartan	Gabapentin	3.0 (-27.8 to 33.7)
% loss to followup	Candesartan	Guanfacine	-3.0 (-40.7 to 34.7)
% loss to followup	Candesartan	Lamotrigine	5.0 (-32.7 to 42.7)
% loss to followup	Candesartan	Lisinopril	-17.0 (-54.7 to 20.7)
% loss to followup	Candesartan	Lisuride	5.0 (-32.7 to 42.7)
% loss to followup	Candesartan	Magnesium	-18.0 (-48.8 to 12.8)
% loss to followup	Candesartan	Methysergide	-27.4 (-65.1 to 10.3)
% loss to followup	Candesartan	Mianserin	-5.5 (-43.2 to 32.2)
% loss to followup	Candesartan	Montelukast	2.8 (-34.9 to 40.5)
% loss to followup	Candesartan	Naproxen sodium	-10.0 (-47.7 to 27.7)
% loss to followup	Candesartan	Nicardipine	-9.0 (-46.7 to 28.7)
% loss to followup	Candesartan	Nifedipine	-17.0 (-54.7 to 20.7)
% loss to followup	Candesartan	Nimodipine	-12.7 (-42.5 to 17.1)
% loss to followup	Candesartan	Oxcarbazepine	1.5 (-36.2 to 39.2)
% loss to followup	Candesartan	Propranolol	-9.4 (-37.5 to 18.6)
% loss to followup	Candesartan	Telmisartan	-12.0 (-49.7 to 25.7)
% loss to followup	Candesartan	Tonabersat	-0.1 (-37.8 to 37.6)
% loss to followup	Candesartan	Valproate	1.5 (-31.1 to 34.1)
% loss to followup	Candesartan	Verapamil	-29.0 (-61.6 to 3.6)
% loss to followup	Candesartan	Vigabatrin	5.0 (-32.7 to 42.7)
% loss to followup	Carbamazepine	Clonidine	-16.2 (-44.2 to 11.7)
% loss to followup	Carbamazepine	Dihydroergotamine	5.9 (-24.8 to 36.7)
% loss to followup	Carbamazepine	Divalproex	4.5 (-28.2 to 37.1)
% loss to followup	Carbamazepine	Femoxetine	-17.8 (-47.6 to 12.0)
% loss to followup	Carbamazepine	Fluoxetine	-15.9 (-45.6 to 13.9)
% loss to followup	Carbamazepine	Gabapentin	4.3 (-26.5 to 35.0)
% loss to followup	Carbamazepine	Guanfacine	-1.7 (-39.4 to 36.0)
% loss to followup	Carbamazepine	Lamotrigine	6.3 (-31.4 to 44.0)
% loss to followup	Carbamazepine	Lisinopril	-15.7 (-53.4 to 22.0)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Carbamazepine	Lisuride	6.3 (-31.4 to 44.0)
% loss to followup	Carbamazepine	Magnesium	-16.7 (-47.5 to 14.1)
% loss to followup	Carbamazepine	Methysergide	-26.1 (-63.8 to 11.6)
% loss to followup	Carbamazepine	Mianserin	-4.2 (-41.9 to 33.5)
% loss to followup	Carbamazepine	Montelukast	4.1 (-33.6 to 41.8)
% loss to followup	Carbamazepine	Naproxen sodium	-8.7 (-46.4 to 29.0)
% loss to followup	Carbamazepine	Nicardipine	-7.7 (-45.4 to 30.0)
% loss to followup	Carbamazepine	Nifedipine	-15.7 (-53.4 to 22.0)
% loss to followup	Carbamazepine	Nimodipine	-11.4 (-41.2 to 18.4)
% loss to followup	Carbamazepine	Oxcarbazepine	2.8 (-34.9 to 40.5)
% loss to followup	Carbamazepine	Propranolol	-8.1 (-36.2 to 19.9)
% loss to followup	Carbamazepine	Telmisartan	-10.7 (-48.4 to 27.0)
% loss to followup	Carbamazepine	Tonabersat	1.2 (-36.5 to 38.9)
% loss to followup	Carbamazepine	Valproate	2.8 (-29.8 to 35.4)
% loss to followup	Carbamazepine	Verapamil	-27.7 (-60.3 to 4.9)
% loss to followup	Carbamazepine	Vigabatrin	6.3 (-31.4 to 44.0)
% loss to followup	Clonidine	Dihydroergotamine	22.2 (4.6 to 39.7)
% loss to followup	Clonidine	Divalproex	20.7 (0.1 to 41.3)
% loss to followup	Clonidine	Femoxetine	-1.6 (-17.4 to 14.2)
% loss to followup	Clonidine	Fluoxetine	0.4 (-15.4 to 16.1)
% loss to followup	Clonidine	Gabapentin	20.5 (3.0 to 38.0)
% loss to followup	Clonidine	Guanfacine	14.5 (-13.4 to 42.5)
% loss to followup	Clonidine	Lamotrigine	22.5 (-5.4 to 50.5)
% loss to followup	Clonidine	Lisinopril	0.5 (-27.4 to 28.5)
% loss to followup	Clonidine	Lisuride	22.5 (-5.4 to 50.5)
% loss to followup	Clonidine	Magnesium	-0.5 (-18.0 to 17.1)
% loss to followup	Clonidine	Methysergide	-9.9 (-37.8 to 18.1)
% loss to followup	Clonidine	Mianserin	12.0 (-15.9 to 40.0)
% loss to followup	Clonidine	Montelukast	20.3 (-7.6 to 48.3)
% loss to followup	Clonidine	Naproxen sodium	7.5 (-20.4 to 35.5)
% loss to followup	Clonidine	Nicardipine	8.5 (-19.4 to 36.5)
% loss to followup	Clonidine	Nifedipine	0.5 (-27.4 to 28.5)
% loss to followup	Clonidine	Nimodipine	4.9 (-10.9 to 20.6)
% loss to followup	Clonidine	Oxcarbazepine	19.0 (-8.9 to 47.0)
% loss to followup	Clonidine	Propranolol	8.1 (-4.2 to 20.3)
% loss to followup	Clonidine	Telmisartan	5.5 (-22.4 to 33.5)
% loss to followup	Clonidine	Tonabersat	17.4 (-10.5 to 45.4)
% loss to followup	Clonidine	Valproate	19.0 (-1.6 to 39.7)
% loss to followup	Clonidine	Verapamil	-11.5 (-32.1 to 9.2)
% loss to followup	Clonidine	Vigabatrin	22.5 (-5.4 to 50.5)
% loss to followup	Dihydroergotamine	Divalproex	-1.5 (-25.8 to 22.9)
% loss to followup	Dihydroergotamine	Femoxetine	-23.8 (-44.1 to -3.4)
% loss to followup	Dihydroergotamine	Fluoxetine	-21.8 (-42.1 to -1.4)
% loss to followup	Dihydroergotamine	Gabapentin	-1.7 (-23.4 to 20.1)
% loss to followup	Dihydroergotamine	Guanfacine	-7.6 (-38.4 to 23.1)
% loss to followup	Dihydroergotamine	Lamotrigine	0.4 (-30.4 to 31.1)
% loss to followup	Dihydroergotamine	Lisinopril	-21.6 (-52.4 to 9.1)
% loss to followup	Dihydroergotamine	Lisuride	0.4 (-30.4 to 31.1)
% loss to followup	Dihydroergotamine	Magnesium	-22.6 (-44.4 to -0.9)
% loss to followup	Dihydroergotamine	Methysergide	-32.0 (-62.8 to -1.3)
% loss to followup	Dihydroergotamine	Mianserin	-10.1 (-40.9 to 20.6)
% loss to followup	Dihydroergotamine	Montelukast	-1.8 (-32.6 to 28.9)
% loss to followup	Dihydroergotamine	Naproxen sodium	-14.6 (-45.4 to 16.1)
% loss to followup	Dihydroergotamine	Nicardipine	-13.6 (-44.4 to 17.1)
% loss to followup	Dihydroergotamine	Nifedipine	-21.6 (-52.4 to 9.1)
% loss to followup	Dihydroergotamine	Nimodipine	-17.3 (-37.7 to 3.0)
% loss to followup	Dihydroergotamine	Oxcarbazepine	-3.1 (-33.9 to 27.6)
% loss to followup	Dihydroergotamine	Propranolol	-14.1 (-31.8 to 3.7)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Dihydroergotamine	Telmisartan	-16.6 (-47.4 to 14.1)
% loss to followup	Dihydroergotamine	Tonabersat	-4.7 (-35.5 to 26.0)
% loss to followup	Dihydroergotamine	Valproate	-3.1 (-27.5 to 21.2)
% loss to followup	Dihydroergotamine	Verapamil	-33.6 (-58.0 to -9.3)
% loss to followup	Dihydroergotamine	Vigabatrin	0.4 (-30.4 to 31.1)
% loss to followup	Divalproex	Femoxetine	-22.3 (-45.4 to 0.8)
% loss to followup	Divalproex	Fluoxetine	-20.3 (-43.4 to 2.7)
% loss to followup	Divalproex	Gabapentin	-0.2 (-24.5 to 24.1)
% loss to followup	Divalproex	Guanfacine	-6.2 (-38.8 to 26.5)
% loss to followup	Divalproex	Lamotrigine	1.8 (-30.8 to 34.5)
% loss to followup	Divalproex	Lisinopril	-20.2 (-52.8 to 12.5)
% loss to followup	Divalproex	Lisuride	1.8 (-30.8 to 34.5)
% loss to followup	Divalproex	Magnesium	-21.2 (-45.5 to 3.1)
% loss to followup	Divalproex	Methysergide	-30.6 (-63.2 to 2.1)
% loss to followup	Divalproex	Mianserin	-8.7 (-41.3 to 24.0)
% loss to followup	Divalproex	Montelukast	-0.4 (-33.0 to 32.3)
% loss to followup	Divalproex	Naproxen sodium	-13.2 (-45.8 to 19.5)
% loss to followup	Divalproex	Nicardipine	-12.2 (-44.8 to 20.5)
% loss to followup	Divalproex	Nifedipine	-20.2 (-52.8 to 12.5)
% loss to followup	Divalproex	Nimodipine	-15.9 (-38.9 to 7.2)
% loss to followup	Divalproex	Oxcarbazepine	-1.7 (-34.3 to 31.0)
% loss to followup	Divalproex	Propranolol	-12.6 (-33.4 to 8.2)
% loss to followup	Divalproex	Telmisartan	-15.2 (-47.8 to 17.5)
% loss to followup	Divalproex	Tonabersat	-3.3 (-35.9 to 29.4)
% loss to followup	Divalproex	Valproate	-1.7 (-28.3 to 25.0)
% loss to followup	Divalproex	Verapamil	-32.2 (-58.8 to -5.5)
% loss to followup	Divalproex	Vigabatrin	1.8 (-30.8 to 34.5)
% loss to followup	Femoxetine	Fluoxetine	2.0 (-16.9 to 20.8)
% loss to followup	Femoxetine	Gabapentin	22.1 (1.7 to 42.4)
% loss to followup	Femoxetine	Guanfacine	16.1 (-13.7 to 45.9)
% loss to followup	Femoxetine	Lamotrigine	24.1 (-5.7 to 53.9)
% loss to followup	Femoxetine	Lisinopril	2.1 (-27.7 to 31.9)
% loss to followup	Femoxetine	Lisuride	24.1 (-5.7 to 53.9)
% loss to followup	Femoxetine	Magnesium	1.1 (-19.2 to 21.5)
% loss to followup	Femoxetine	Methysergide	-8.3 (-38.1 to 21.5)
% loss to followup	Femoxetine	Mianserin	13.6 (-16.2 to 43.4)
% loss to followup	Femoxetine	Montelukast	21.9 (-7.9 to 51.7)
% loss to followup	Femoxetine	Naproxen sodium	9.1 (-20.7 to 38.9)
% loss to followup	Femoxetine	Nicardipine	10.1 (-19.7 to 39.9)
% loss to followup	Femoxetine	Nifedipine	2.1 (-27.7 to 31.9)
% loss to followup	Femoxetine	Nimodipine	6.5 (-12.4 to 25.3)
% loss to followup	Femoxetine	Oxcarbazepine	20.6 (-9.2 to 50.4)
% loss to followup	Femoxetine	Propranolol	9.7 (-6.3 to 25.7)
% loss to followup	Femoxetine	Telmisartan	7.1 (-22.7 to 36.9)
% loss to followup	Femoxetine	Tonabersat	19.0 (-10.8 to 48.8)
% loss to followup	Femoxetine	Valproate	20.6 (-2.4 to 43.7)
% loss to followup	Femoxetine	Verapamil	-9.9 (-32.9 to 13.2)
% loss to followup	Femoxetine	Vigabatrin	24.1 (-5.7 to 53.9)
% loss to followup	Fluoxetine	Gabapentin	20.1 (-0.2 to 40.5)
% loss to followup	Fluoxetine	Guanfacine	14.2 (-15.6 to 43.9)
% loss to followup	Fluoxetine	Lamotrigine	22.2 (-7.6 to 51.9)
% loss to followup	Fluoxetine	Lisinopril	0.2 (-29.6 to 29.9)
% loss to followup	Fluoxetine	Lisuride	22.2 (-7.6 to 51.9)
% loss to followup	Fluoxetine	Magnesium	-0.9 (-21.2 to 19.5)
% loss to followup	Fluoxetine	Methysergide	-10.3 (-40.0 to 19.5)
% loss to followup	Fluoxetine	Mianserin	11.7 (-18.1 to 41.4)
% loss to followup	Fluoxetine	Montelukast	20.0 (-9.8 to 49.7)
% loss to followup	Fluoxetine	Naproxen sodium	7.2 (-22.6 to 36.9)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Fluoxetine	Nicardipine	8.2 (-21.6 to 37.9)
% loss to followup	Fluoxetine	Nifedipine	0.2 (-29.6 to 29.9)
% loss to followup	Fluoxetine	Nimodipine	4.5 (-14.4 to 23.3)
% loss to followup	Fluoxetine	Oxcarbazepine	18.7 (-11.1 to 48.4)
% loss to followup	Fluoxetine	Propranolol	7.7 (-8.3 to 23.7)
% loss to followup	Fluoxetine	Telmisartan	5.2 (-24.6 to 34.9)
% loss to followup	Fluoxetine	Tonabersat	17.1 (-12.7 to 46.8)
% loss to followup	Fluoxetine	Valproate	18.7 (-4.4 to 41.7)
% loss to followup	Fluoxetine	Verapamil	-11.9 (-34.9 to 11.2)
% loss to followup	Fluoxetine	Vigabatrin	22.2 (-7.6 to 51.9)
% loss to followup	Gabapentin	Guanfacine	-6.0 (-36.7 to 24.8)
% loss to followup	Gabapentin	Lamotrigine	2.0 (-28.7 to 32.8)
% loss to followup	Gabapentin	Lisinopril	-20.0 (-50.7 to 10.8)
% loss to followup	Gabapentin	Lisuride	2.0 (-28.7 to 32.8)
% loss to followup	Gabapentin	Magnesium	-21.0 (-42.7 to 0.8)
% loss to followup	Gabapentin	Methysergide	-30.4 (-61.1 to 0.4)
% loss to followup	Gabapentin	Mianserin	-8.5 (-39.2 to 22.3)
% loss to followup	Gabapentin	Montelukast	-0.2 (-30.9 to 30.6)
% loss to followup	Gabapentin	Naproxen sodium	-13.0 (-43.7 to 17.8)
% loss to followup	Gabapentin	Nicardipine	-12.0 (-42.7 to 18.8)
% loss to followup	Gabapentin	Nifedipine	-20.0 (-50.7 to 10.8)
% loss to followup	Gabapentin	Nimodipine	-15.6 (-36.0 to 4.7)
% loss to followup	Gabapentin	Oxcarbazepine	-1.5 (-32.2 to 29.3)
% loss to followup	Gabapentin	Propranolol	-12.4 (-30.2 to 5.4)
% loss to followup	Gabapentin	Telmisartan	-15.0 (-45.7 to 15.8)
% loss to followup	Gabapentin	Tonabersat	-3.1 (-33.8 to 27.7)
% loss to followup	Gabapentin	Valproate	-1.5 (-25.8 to 22.9)
% loss to followup	Gabapentin	Verapamil	-32.0 (-56.3 to -7.6)
% loss to followup	Gabapentin	Vigabatrin	2.0 (-28.7 to 32.8)
% loss to followup	Guanfacine	Lamotrigine	8.0 (-29.7 to 45.7)
% loss to followup	Guanfacine	Lisinopril	-14.0 (-51.7 to 23.7)
% loss to followup	Guanfacine	Lisuride	8.0 (-29.7 to 45.7)
% loss to followup	Guanfacine	Magnesium	-15.0 (-45.8 to 15.8)
% loss to followup	Guanfacine	Methysergide	-24.4 (-62.1 to 13.3)
% loss to followup	Guanfacine	Mianserin	-2.5 (-40.2 to 35.2)
% loss to followup	Guanfacine	Montelukast	5.8 (-31.9 to 43.5)
% loss to followup	Guanfacine	Naproxen sodium	-7.0 (-44.7 to 30.7)
% loss to followup	Guanfacine	Nicardipine	-6.0 (-43.7 to 31.7)
% loss to followup	Guanfacine	Nifedipine	-14.0 (-51.7 to 23.7)
% loss to followup	Guanfacine	Nimodipine	-9.7 (-39.5 to 20.1)
% loss to followup	Guanfacine	Oxcarbazepine	4.5 (-33.2 to 42.2)
% loss to followup	Guanfacine	Propranolol	-6.4 (-34.5 to 21.6)
% loss to followup	Guanfacine	Telmisartan	-9.0 (-46.7 to 28.7)
% loss to followup	Guanfacine	Tonabersat	2.9 (-34.8 to 40.6)
% loss to followup	Guanfacine	Valproate	4.5 (-28.1 to 37.1)
% loss to followup	Guanfacine	Verapamil	-26.0 (-58.6 to 6.6)
% loss to followup	Guanfacine	Vigabatrin	8.0 (-29.7 to 45.7)
% loss to followup	Lamotrigine	Lisinopril	-22.0 (-59.7 to 15.7)
% loss to followup	Lamotrigine	Lisuride	0.0 (-37.7 to 37.7)
% loss to followup	Lamotrigine	Magnesium	-23.0 (-53.8 to 7.8)
% loss to followup	Lamotrigine	Methysergide	-32.4 (-70.1 to 5.3)
% loss to followup	Lamotrigine	Mianserin	-10.5 (-48.2 to 27.2)
% loss to followup	Lamotrigine	Montelukast	-2.2 (-39.9 to 35.5)
% loss to followup	Lamotrigine	Naproxen sodium	-15.0 (-52.7 to 22.7)
% loss to followup	Lamotrigine	Nicardipine	-14.0 (-51.7 to 23.7)
% loss to followup	Lamotrigine	Nifedipine	-22.0 (-59.7 to 15.7)
% loss to followup	Lamotrigine	Nimodipine	-17.7 (-47.5 to 12.1)
% loss to followup	Lamotrigine	Oxcarbazepine	-3.5 (-41.2 to 34.2)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Lamotrigine	Propranolol	-14.4 (-42.5 to 13.6)
% loss to followup	Lamotrigine	Telmisartan	-17.0 (-54.7 to 20.7)
% loss to followup	Lamotrigine	Tonabersat	-5.1 (-42.8 to 32.6)
% loss to followup	Lamotrigine	Valproate	-3.5 (-36.1 to 29.1)
% loss to followup	Lamotrigine	Verapamil	-34.0 (-66.6 to -1.4)
% loss to followup	Lamotrigine	Vigabatrin	0.0 (-37.7 to 37.7)
% loss to followup	Lisinopril	Lisuride	22.0 (-15.7 to 59.7)
% loss to followup	Lisinopril	Magnesium	-1.0 (-31.8 to 29.8)
% loss to followup	Lisinopril	Methysergide	-10.4 (-48.1 to 27.3)
% loss to followup	Lisinopril	Mianserin	11.5 (-26.2 to 49.2)
% loss to followup	Lisinopril	Montelukast	19.8 (-17.9 to 57.5)
% loss to followup	Lisinopril	Naproxen sodium	7.0 (-30.7 to 44.7)
% loss to followup	Lisinopril	Nicardipine	8.0 (-29.7 to 45.7)
% loss to followup	Lisinopril	Nifedipine	0.0 (-37.7 to 37.7)
% loss to followup	Lisinopril	Nimodipine	4.3 (-25.5 to 34.1)
% loss to followup	Lisinopril	Oxcarbazepine	18.5 (-19.2 to 56.2)
% loss to followup	Lisinopril	Propranolol	7.6 (-20.5 to 35.6)
% loss to followup	Lisinopril	Telmisartan	5.0 (-32.7 to 42.7)
% loss to followup	Lisinopril	Tonabersat	16.9 (-20.8 to 54.6)
% loss to followup	Lisinopril	Valproate	18.5 (-14.1 to 51.1)
% loss to followup	Lisinopril	Verapamil	-12.0 (-44.6 to 20.6)
% loss to followup	Lisinopril	Vigabatrin	22.0 (-15.7 to 59.7)
% loss to followup	Lisuride	Magnesium	-23.0 (-53.8 to 7.8)
% loss to followup	Lisuride	Methysergide	-32.4 (-70.1 to 5.3)
% loss to followup	Lisuride	Mianserin	-10.5 (-48.2 to 27.2)
% loss to followup	Lisuride	Montelukast	-2.2 (-39.9 to 35.5)
% loss to followup	Lisuride	Naproxen sodium	-15.0 (-52.7 to 22.7)
% loss to followup	Lisuride	Nicardipine	-14.0 (-51.7 to 23.7)
% loss to followup	Lisuride	Nifedipine	-22.0 (-59.7 to 15.7)
% loss to followup	Lisuride	Nimodipine	-17.7 (-47.5 to 12.1)
% loss to followup	Lisuride	Oxcarbazepine	-3.5 (-41.2 to 34.2)
% loss to followup	Lisuride	Propranolol	-14.4 (-42.5 to 13.6)
% loss to followup	Lisuride	Telmisartan	-17.0 (-54.7 to 20.7)
% loss to followup	Lisuride	Tonabersat	-5.1 (-42.8 to 32.6)
% loss to followup	Lisuride	Valproate	-3.5 (-36.1 to 29.1)
% loss to followup	Lisuride	Verapamil	-34.0 (-66.6 to -1.4)
% loss to followup	Lisuride	Vigabatrin	0.0 (-37.7 to 37.7)
% loss to followup	Magnesium	Mianserin	12.5 (-18.3 to 43.3)
% loss to followup	Magnesium	Montelukast	20.8 (-10.0 to 51.6)
% loss to followup	Magnesium	Naproxen sodium	8.0 (-22.8 to 38.8)
% loss to followup	Magnesium	Nicardipine	9.0 (-21.8 to 39.8)
% loss to followup	Magnesium	Nifedipine	1.0 (-29.8 to 31.8)
% loss to followup	Magnesium	Nimodipine	5.3 (-15.0 to 25.7)
% loss to followup	Magnesium	Oxcarbazepine	19.5 (-11.3 to 50.3)
% loss to followup	Magnesium	Propranolol	8.6 (-9.2 to 26.3)
% loss to followup	Magnesium	Telmisartan	6.0 (-24.8 to 36.8)
% loss to followup	Magnesium	Tonabersat	17.9 (-12.9 to 48.7)
% loss to followup	Magnesium	Valproate	19.5 (-4.8 to 43.8)
% loss to followup	Magnesium	Verapamil	-11.0 (-35.3 to 13.3)
% loss to followup	Magnesium	Vigabatrin	23.0 (-7.8 to 53.8)
% loss to followup	Methysergide	Magnesium	9.4 (-21.4 to 40.2)
% loss to followup	Methysergide	Mianserin	21.9 (-15.8 to 59.6)
% loss to followup	Methysergide	Montelukast	30.2 (-7.5 to 67.9)
% loss to followup	Methysergide	Naproxen sodium	17.4 (-20.3 to 55.1)
% loss to followup	Methysergide	Nicardipine	18.4 (-19.3 to 56.1)
% loss to followup	Methysergide	Nifedipine	10.4 (-27.3 to 48.1)
% loss to followup	Methysergide	Nimodipine	14.7 (-15.1 to 44.5)
% loss to followup	Methysergide	Oxcarbazepine	28.9 (-8.8 to 66.6)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Methysergide	Propranolol	18.0 (-10.1 to 46.0)
% loss to followup	Methysergide	Telmisartan	15.4 (-22.3 to 53.1)
% loss to followup	Methysergide	Tonabersat	27.3 (-10.4 to 65.0)
% loss to followup	Methysergide	Valproate	28.9 (-3.7 to 61.5)
% loss to followup	Methysergide	Verapamil	-1.6 (-34.2 to 31.0)
% loss to followup	Methysergide	Vigabatrin	32.4 (-5.3 to 70.1)
% loss to followup	Mianserin	Montelukast	8.3 (-29.4 to 46.0)
% loss to followup	Mianserin	Naproxen sodium	-4.5 (-42.2 to 33.2)
% loss to followup	Mianserin	Nicardipine	-3.5 (-41.2 to 34.2)
% loss to followup	Mianserin	Nifedipine	-11.5 (-49.2 to 26.2)
% loss to followup	Mianserin	Nimodipine	-7.2 (-37.0 to 22.6)
% loss to followup	Mianserin	Oxcarbazepine	7.0 (-30.7 to 44.7)
% loss to followup	Mianserin	Propranolol	-3.9 (-32.0 to 24.1)
% loss to followup	Mianserin	Telmisartan	-6.5 (-44.2 to 31.2)
% loss to followup	Mianserin	Tonabersat	5.4 (-32.3 to 43.1)
% loss to followup	Mianserin	Valproate	7.0 (-25.6 to 39.6)
% loss to followup	Mianserin	Verapamil	-23.5 (-56.1 to 9.1)
% loss to followup	Mianserin	Vigabatrin	10.5 (-27.2 to 48.2)
% loss to followup	Montelukast	Naproxen sodium	-12.8 (-50.5 to 24.9)
% loss to followup	Montelukast	Nicardipine	-11.8 (-49.5 to 25.9)
% loss to followup	Montelukast	Nifedipine	-19.8 (-57.5 to 17.9)
% loss to followup	Montelukast	Nimodipine	-15.5 (-45.3 to 14.3)
% loss to followup	Montelukast	Oxcarbazepine	-1.3 (-39.0 to 36.4)
% loss to followup	Montelukast	Propranolol	-12.2 (-40.3 to 15.8)
% loss to followup	Montelukast	Telmisartan	-14.8 (-52.5 to 22.9)
% loss to followup	Montelukast	Tonabersat	-2.9 (-40.6 to 34.8)
% loss to followup	Montelukast	Valproate	-1.3 (-33.9 to 31.3)
% loss to followup	Montelukast	Verapamil	-31.8 (-64.4 to 0.8)
% loss to followup	Montelukast	Vigabatrin	2.2 (-35.5 to 39.9)
% loss to followup	Naproxen sodium	Nicardipine	1.0 (-36.7 to 38.7)
% loss to followup	Naproxen sodium	Nifedipine	-7.0 (-44.7 to 30.7)
% loss to followup	Naproxen sodium	Nimodipine	-2.7 (-32.5 to 27.1)
% loss to followup	Naproxen sodium	Oxcarbazepine	11.5 (-26.2 to 49.2)
% loss to followup	Naproxen sodium	Propranolol	0.6 (-27.5 to 28.6)
% loss to followup	Naproxen sodium	Telmisartan	-2.0 (-39.7 to 35.7)
% loss to followup	Naproxen sodium	Tonabersat	9.9 (-27.8 to 47.6)
% loss to followup	Naproxen sodium	Valproate	11.5 (-21.1 to 44.1)
% loss to followup	Naproxen sodium	Verapamil	-19.0 (-51.6 to 13.6)
% loss to followup	Naproxen sodium	Vigabatrin	15.0 (-22.7 to 52.7)
% loss to followup	Nicardipine	Nifedipine	-8.0 (-45.7 to 29.7)
% loss to followup	Nicardipine	Nimodipine	-3.7 (-33.5 to 26.1)
% loss to followup	Nicardipine	Oxcarbazepine	10.5 (-27.2 to 48.2)
% loss to followup	Nicardipine	Propranolol	-0.4 (-28.5 to 27.6)
% loss to followup	Nicardipine	Telmisartan	-3.0 (-40.7 to 34.7)
% loss to followup	Nicardipine	Tonabersat	8.9 (-28.8 to 46.6)
% loss to followup	Nicardipine	Valproate	10.5 (-22.1 to 43.1)
% loss to followup	Nicardipine	Verapamil	-20.0 (-52.6 to 12.6)
% loss to followup	Nicardipine	Vigabatrin	14.0 (-23.7 to 51.7)
% loss to followup	Nifedipine	Nimodipine	4.3 (-25.5 to 34.1)
% loss to followup	Nifedipine	Oxcarbazepine	18.5 (-19.2 to 56.2)
% loss to followup	Nifedipine	Propranolol	7.6 (-20.5 to 35.6)
% loss to followup	Nifedipine	Telmisartan	5.0 (-32.7 to 42.7)
% loss to followup	Nifedipine	Tonabersat	16.9 (-20.8 to 54.6)
% loss to followup	Nifedipine	Valproate	18.5 (-14.1 to 51.1)
% loss to followup	Nifedipine	Verapamil	-12.0 (-44.6 to 20.6)
% loss to followup	Nifedipine	Vigabatrin	22.0 (-15.7 to 59.7)
% loss to followup	Nimodipine	Oxcarbazepine	14.2 (-15.6 to 44.0)
% loss to followup	Nimodipine	Propranolol	3.2 (-12.8 to 19.2)

Appendix Table D6. Differences in subject characteristics in randomized controlled clinical trials that examined efficacy of the drugs for migraine prevention in adults (differences are statistically significant when 95% CI do not include 0) (continued)

% loss to followup	Nimodipine	Telmisartan	0.7 (-29.1 to 30.5)
% loss to followup	Nimodipine	Tonabersat	12.6 (-17.2 to 42.4)
% loss to followup	Nimodipine	Valproate	14.2 (-8.9 to 37.2)
% loss to followup	Nimodipine	Verapamil	-16.3 (-39.4 to 6.7)
% loss to followup	Nimodipine	Vigabatrin	17.7 (-12.1 to 47.5)
% loss to followup	Oxcarbazepine	Propranolol	-10.9 (-39.0 to 17.1)
% loss to followup	Oxcarbazepine	Telmisartan	-13.5 (-51.2 to 24.2)
% loss to followup	Oxcarbazepine	Tonabersat	-1.6 (-39.3 to 36.1)
% loss to followup	Oxcarbazepine	Valproate	0.0 (-32.6 to 32.6)
% loss to followup	Oxcarbazepine	Verapamil	-30.5 (-63.1 to 2.1)
% loss to followup	Oxcarbazepine	Vigabatrin	3.5 (-34.2 to 41.2)
% loss to followup	Propranolol	Telmisartan	-2.6 (-30.6 to 25.5)
% loss to followup	Propranolol	Tonabersat	9.3 (-18.7 to 37.4)
% loss to followup	Propranolol	Valproate	10.9 (-9.9 to 31.8)
% loss to followup	Propranolol	Verapamil	-19.6 (-40.4 to 1.3)
% loss to followup	Propranolol	Vigabatrin	14.4 (-13.6 to 42.5)
% loss to followup	Telmisartan	Tonabersat	11.9 (-25.8 to 49.6)
% loss to followup	Telmisartan	Valproate	13.5 (-19.1 to 46.1)
% loss to followup	Telmisartan	Verapamil	-17.0 (-49.6 to 15.6)
% loss to followup	Telmisartan	Vigabatrin	17.0 (-20.7 to 54.7)
% loss to followup	Tonabersat	Valproate	1.6 (-31.0 to 34.2)
% loss to followup	Tonabersat	Verapamil	-28.9 (-61.5 to 3.7)
% loss to followup	Tonabersat	Vigabatrin	5.1 (-32.6 to 42.8)
% loss to followup	Valproate	Verapamil	-30.5 (-57.1 to -3.9)
% loss to followup	Valproate	Vigabatrin	3.5 (-29.1 to 36.1)
% loss to followup	Verapamil	Vigabatrin	34.0 (1.4 to 66.6)

Appendix Table D7. Risk of bias in randomized controlled clinical trials of drugs for migraine prevention in adults

	Adequate Allocation Conceal-ment	Unclear Allocation Conceal-ment	Randomi-zation Adequate	Unclear Adequacy of Random-ization	Random-ized In-adequate	Planned Inten-tion to-treat	No Planned Intention to- treat	Double Blind	Single Blind	Open Label	Low ROB	Medium ROB	High ROB	Unclear ROB	Total
Topiramate*	6	21	15	7	5	15	12	25	0	2	12	14	1	0	27
Divalproex*	0	3	3	0	0	2	1	3	0	0	2	1	0	0	3
Propranolol*	1	44	13	32	0	6	39	39	2	4	6	34	5	0	45
Timolol*	0	2	0	1	1	1	1	2	0	0	0	2	0	0	2
Acetazolamide	1	0	1	0	0	1	0	1	0	0	1	0	0	0	1
Gabapentin	1	3	1	2	1	2	2	4	0	0	1	3	0	0	4
Lamotrigine	0	1	0	1	0	1	0	1	0	0	1	0	0	0	1
Oxcarbazepine	1	0	1	0	0	1	0	1	0	0	1	0	0	0	1
Valproate	0	4	2	2	0	1	3	3	0	1	1	2	1	0	4
Vigabatrin	0	1	0	1	0	0	1	1	0	0	0	1	0	0	1
Carbamazepine	0	1	0	1	0	0	1	1	0	0	0	1	0	0	1
Alprenolol	0	1	0	1	0	0	1	1	0	0	0	1	0	0	1
Atenolol	0	2	0	2	0	0	2	2	0	0	0	2	0	0	2
Bisoprolol	0	1	1	0	0	1	0	1	0	0	0	1	0	0	1
Metoprolol	0	9	3	5	1	2	7	9	0	0	1	8	0	0	9
Nadolol	0	2	0	2	0	1	1	2	0	0	1	1	0	0	2
Pindolol	0	2	1	1	0	0	2	2	0	0	0	2	0	0	2
Acebutolol	0	1	0	1	0	0	1	1	0	0	0	1	0	0	1
Amitriptyline	0	4	3	1	0	1	3	3	0	1	0	4	0	0	4
Femoxetine	0	6	3	3	0	0	6	6	0	0	0	6	0	0	6
Fluoxetine	0	6	4	1	1	0	6	5	0	1	0	5	1	0	6
Fluvoxamine	0	1	1	0	0	0	1	1	0	0	0	1	0	0	1
Venlafaxine	0	3	2	0	1	1	2	2	0	1	0	2	1	0	3
Mianserin	0	1	0	0	1	0	1	1	0	0	0	0	1	0	1
Captopril	0	1	0	1	0	0	1	1	0	0	1	0	0	0	1
Lisinopril	1	0	0	1	0	1	0	1	0	0	1	0	0	0	1
Candesartan	1	0	0	1	0	1	0	1	0	0	1	0	0	0	1
Telmisartan	0	1	0	0	1	0	1	1	0	0	0	0	1	0	1
Nifedipine	0	1	0	1	0	0	1	1	0	0	0	1	0	0	1
Nimodipine	0	6	1	4	1	1	5	5	1	0	0	5	1	0	6
Verapamil	0	2	0	2	0	0	2	2	0	0	0	2	0	0	2
Nicardipine	0	1	1	0	0	0	1	1	0	0	0	1	0	0	1
Clonidine	0	14	1	13	0	0	14	13	0	1	3	9	1	1	14
Guanfacine	0	1	0	1	0	1	0	1	0	0	1	0	0	0	1
Dihydro-ergocryptine	0	3	0	2	1	0	3	3	0	0	0	2	1	0	3

Appendix Table D7. Risk of bias in randomized controlled clinical trials of drugs for migraine prevention in adults (continued)

	Adequate Allocation Conceal-ment	Unclear Allocation Conceal-ment	Randomi-zation Adequate	Unclear Adequacy of Random-ization	Random-ized In-adequate	Planned Inten-tion to-treat	No Planned Intention to- treat	Double Blind	Single Blind	Open Label	Low ROB	Medium ROB	High ROB	Unclear ROB	Total
Dihydro-ergotamine	0	4	2	2	0	1	3	3	0	1	1	3	0	0	4
Lisuride	0	3	2	1	0	0	3	3	0	0	0	3	0	0	3
Methysergide	0	2	0	2	0	0	2	2	0	0	0	2	0	0	2
Non -drug	2	2	3	0	1	3	1	0	1	3	1	2	1	0	4
Aspirin	0	5	1	3	1	1	4	5	0	0	2	3	0	0	5
Fenoprofen	0	1	0	0	1	0	1	0	0	1	0	1	0	0	1
Flurbiprofen	0	1	0	1	0	0	1	0	0	1	0	1	0	0	1
Indobufen	0	1	1	0	0	0	1	1	0	0	1	0	0	0	1
Indomethacin	0	1	0	1	0	1	0	0	0	1	0	1	0	0	1
Induprofen	0	1	1	0	0	0	1	0	0	1	0	1	0	0	1
Ketoprofen	0	1	0	1	0	0	1	0	0	1	0	1	0	0	1
Naproxen	0	3	1	1	1	0	3	0	0	3	0	0	2	1	3
Rofecoxib	0	1	1	0	0	1	0	1	0	0	0	1	0	0	1
Tolfenamic Acid	0	1	0	1	0	0	1	0	0	1	0	1	0	0	1
Magnesium	0	3	2	0	1	2	1	3	0	0	2	0	1	0	3
Montelukast	0	1	1	0	0	1	0	1	0	0	1	0	0	0	1
Tizanidine	0	1	1	0	0	0	1	1	0	0	0	1	0	0	1
Tonabersat	0	1	1	0	0	1	0	1	0	0	1	0	0	0	1
Total	14	206	87	111	22	53	167	188	5	27	45	148	25	2	220**
%	6.36	93.64	39.55	50.45	10	24.09	75.91	85.45	2.27	12.27	20.45	67.27	11.36	0.91	100

* approved drugs;**- 24 RCTs of flunarizine contributed to counts; ROB = risk of bias

Appendix Table D8. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Trial	Country	Sample [Number Analyzed] % Women	Mean Age	Definition of Migraine	% Without Aura	Duration of Migraine, Months	Baseline Severity	Treatment History
Aurora, 2010[1]	PREEMPT NCT00156910	North American	679 [679] 87.5% women	41.7	ICHD-II (2004) section 1, migraine, with the exception of "complicated migraine" (i.e., hemiplegic migraine, basilar-type migraine, ophthalmoplegic migraine, migrainous infarction)	NR % without aura NR	20.4	Migraine episodes: 12.1	% with prior preventive treatments 61.8
Diener, 2010[2] Lipton, 2011[3]	PREEMPT NCT00168428	North America & 16 European	705 [705] 85.4% women	41	ICHD-II (2004) section 1, migraine, with the exception of "complicated migraine"	NR % without aura NR	18	Migraine episodes: 12.1	% with prior preventive treatments 65.1
Saper, 2007[4]	BoNTA-009 Study Group	USA	232 [232] 85.8% women	43.6	Migraine headaches as defined by the International Headache Society criteria	Included % without aura NR	23.8	Migraines per month (historical): 5.7	% with prior preventive treatments NR
Freitag, 2008[5]		USA	60 [41] 73% women	42.3	Migraine episodes meeting the criteria 1.1 or 1.2 of the ICHD-I	NR % without aura NR	NR	Number of migraine episodes: 14.2	% with prior preventive treatments NR
Silberstein, 2000[6]	BOTOX Migraine Clinical Research Group	USA	123 [123] 85.4% women	44	Migraine, International Headache Society guideline	Included % without aura NR	NR	Mean migraine frequency: 4.4	% with prior preventive treatments NR
Elkind, 2006[7]	BoNTA-024-026-036 Study Group	USA	418 [418] 84.7% women	44.1	Migraine, International Headache Society guideline	Included % without aura 50	21	Mean Migraine Headache Frequency: 5.5	% with prior preventive treatments NR
Chankrachang*, 2011[8]	NCT00258609*	Thailand	128 [Vary] 94.4% women	38.6	International Headache Society	% without aura 100	8.2	Migraine attacks per month: 5.1	% with prior preventive

Appendix Table D8. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Trial	Country	Sample [Number Analyzed] % Women	Mean Age	Definition of Migraine	% Without Aura	Duration of Migraine, Months	Baseline Severity	Treatment History
									treatments 98.5
Petri*, 2009[9]	Dysport *Migraine Study Group	Germany	127 [122] 83.6% women	46.2	International Headache Society	Included % without aura NR	26.5	Mean attack frequency per month: 4.8	% with prior preventive treatments NR
Mathew, 2005[10]	BOTOX CDH Study Group	USA	355 [355] 84.5% women	43.5	International Headache Society	Included % without aura NR	Years since onset of chronic daily headache: 14.5	Frequency of migraines/probable migraines (month): 11	% with prior preventive treatments 35.8
Silberstein, 2005[11]		North American	702 [702] 82.9% women	43.4	International Headache Society	Included % without aura NR	Years since onset of CDH: 13.7	Frequency of migraines/probable migraines (month): 10.5	% with prior preventive treatments 49.6
Anand, 2006[12]		India	32 [32] 75% women	NR	International Headache Society	Included % without aura NR	NR	Mean number of headache days per month: 8.3	% with prior preventive treatments NR
Cady, 2008[13]		USA	59 [54] 85.2% women	42.1	International Headache Society	Included % without aura 40.6	NR	Mean headache frequency=5.1; headache days=8.4	% with prior preventive treatments 100
Vo, 2007[14]	Walter Reed Army Medical Center Neurology trial	USA	32 [32] 84.4% women	42.4	International Headache Society	Included % without aura NR	19.5	Mean migraine frequency (days): 19.4	% with prior preventive treatments NR
Aurora, 2007[15]	BOTOX North American Episodic Migraine Study Group	North American	369 [369] 89.2% women	45	International Headache Society	Included % without aura NR	22.7	Migraine headache episodes per month: 6.5	% with prior preventive treatments 38.2
Barrientos, 2003[16]		Chile (Unclear)	30 [30] 80% women	41.1	International Headache Society	Included % without aura NR	15.1	Frequency of migraine attacks (month): 5.1	% with prior preventive treatments NR

Appendix Table D8. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Trial	Country	Sample [Number Analyzed] % Women	Mean Age	Definition of Migraine	% Without Aura	Duration of Migraine, Months	Baseline Severity	Treatment History
Relja, 2007[17]	European BoNTA Headache Study Group	European countries (Belgium, Croatia, Denmark, Finland, France, Germany, Norway, Switzerland, UK)	515 [515] 87.9% women	43.2	International Headache Society	Included % without aura NR	Mean time since first migraine onset (years): 23.1	Mean number of days of acute medication use: 6.2	% with prior preventive treatments 57.6

NR = not reported; * trials of abobotulinumtoxin A

Appendix Table D9. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Finance	Ethical Approval	Consent	Conflict of Interest	Conflict of Interest Disclosure
Aurora, 2010[1]	Industry	Yes	Yes	Yes	SKA has received grants and research support from Advanced Bionics, Alexza, Allergan, Capnia, GlaxoSmithKline, MAP pharmaceuticals, Merck, Ortho-McNeil, Neuralieve, NuPathe and Takeda. She is a consultant for Ortho-McNeil, Merck, GlaxoSmithKline, Allergan, Neuralieve, NuPathe and MAP Pharmaceuticals. She has also received honoraria from Merck, GlaxoSmithKline, Kowa, NuPathe and Ortho-McNeil. DWD has received honoraria from Allergan, Merck, Neuralieve, Coherex, Kowa, Minster, NeurAxon, H Lundbeck, Endo, Pfizer, Nupathe and MAP Pharmaceuticals, in addition to being a consultant to and on the advisory board of these pharmaceutical companies. He has also received funding from Advanced Neurostimulation Systems, St. Jude Medical Center and Medtronic. CCT, RED and MFB are employees of Allergan, and own stock in the company. SDS and RBL have received honoraria and research funding from Allergan, in addition to being consultants to and on the advisory board of Allergan. HCD has received honoraria for participation in clinical trials, contribution to advisory boards, or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Bohringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grunenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brummer, Sanofi-Aventis and Weber & Weber. He has also received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer. Headache research at the Department of Neurology in Essen, where HCD is Professor, is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF), and the European Union.
Diener, 2010[2]	Industry	Yes	Yes	Yes	HCD has received honoraria for participation in clinical trials, contribution to advisory boards and/or oral presentations from Addex Pharma, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid, Bohringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grunenthal, Janssen-Cilag, Lilly, La Roche, 3M Medica, Minster, MSD, Novartis, Johnson & Johnson, Pierre Fabre, Pfizer, Schaper and Brummer, Sanofi-Aventis and Weber & Weber. He has also received financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag and Pfizer. Headache research at the Department of Neurology in Essen, where HCD is professor, is supported by the German Research Council (DFG), the German Ministry of Education and Research (BMBF) and the European Union. DWD has received honoraria from Allergan, Merck, Neuralieve, Coherex, Kowa, Minster, NeurAxon, H Lundbeck, Endo, Pfizer, Nupathe and MAP Pharmaceuticals, in addition to being a consultant to and on the advisory board of these pharmaceutical companies. He has also received funding from Advanced Neurostimulation Systems, St. Jude Medical Center and Medtronic. SKA received grants and research support from Advanced Bionics, Alexza, Allergan, Capnia, GlaxoSmithKline, MAP Pharmaceuticals, Merck, Ortho-McNeil, Neuralieve, NuPathe and Takeda. She is a consultant for Ortho-McNeil, Merck, GlaxoSmithKline, Allergan,

Appendix Table D9. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Finance	Ethical Approval	Consent	Conflict of Interest	Conflict of Interest Disclosure
					Neuralieve, NuPathe and MAP Pharmaceuticals. She has also received honoraria from Merck, GlaxoSmithKline, Kowa, NuPathe and Ortho-McNeil. CCT, RED and MFB are employees of Allergan, and own stock in the company. SDS and RBL have received honoraria and research funding from Allergan, in addition to being consultants to and on the advisory board of Allergan.
Saper, 2007[4]	Industry	No	Yes	Yes	Two authors are employed by Allergan, Inc.
Freitag, 2008[5]	Industry	Yes	Yes	Yes	Dr. Freitag has received grant support and consulting fees from Allergan.
Silberstein, 2000[6]	Industry	Yes	Yes	Yes	One author is employed by Allergan Inc, study funder.
Elkind, 2006[7]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan Inc, study funder.
Chankrachang*, 2011[8]*	Industry	Yes	Yes	No	Not applicable
Petri*, 2009[9]*	Industry	Yes	Yes	Yes	One of the authors (Ceballos-Baumann) has received honoraria for speeches from Ipsen Pharma and from other companies that manufacture botulinum toxin,
Mathew, 2005[10]	Industry	Yes	Yes	Yes	R.Dimitrova, J.Gibson, and C.Turkel are employed by Allergan, Inc., and own stock in the company
Silberstein, 2005[11]	Industry	Yes	Yes	Yes	Dr. Silberstein is on the advisory panel and speakers' bureau and receives research support from Allergan, Inc; Dr Stark has served as a principal investigator and sub investigator for Allergan, Inc, for the past 4 years. Dr Lucas is a consultant for Allergan, Inc. Dr Christie has received a research grant, consultancy fees, and honoraria from Allergan, Inc. Dr Turkel and Mr DeGryse are employed by and own stock in Allergan, Inc.
Anand, 2006[12]	Not reported	Yes	Yes	Not reported	Not applicable
Cady, 2008[13]	Industry	Yes	Yes	Not reported	Not applicable
Vo, 2007[14]	Grant	Yes	Yes	Not reported	Alexander Vo is an employee of Uniformed Services University of the Health Sciences (sponsor of the study)
Aurora, 2007[15]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan, Inc, and own stock in the company.
Barrientos, 2003[16]	Industry	Yes	Yes	Not reported	Not applicable
Relja, 2007[17]	Industry	Yes	Yes	Yes	Two authors are employed by Allergan, Inc. and own stock in the company.

* Trials of abobotulinumtoxin A

Appendix Table D10. Risk of bias in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults

Reference	Masking	Intention to Treat Planned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias	Other Biases
Aurora, 2010[1]	Double blind	Yes	Adequate	No	Unclear	Medium	Mean headache episodes during baseline & Mean migraine episodes during baseline are statistically different between group
Diener, 2010[2]	Double blind	Yes	Adequate	Yes	Unclear	Low	
Saper, 2007[4]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Freitag, 2008[5]	Double blind	Yes	Unclear	Unclear (no tests conducted)	Unclear	Low	Poor reporting quality
Silberstein, 2000[6]	Double blind	Yes	Unclear	No	Unclear	Medium	Mean age differs by group: patients in vehicle group had higher mean age; Baseline frequencies of migraines of any severity were significantly lower in the 75-U BTX-A treatment group (4.40) than in the 25-U BTX-A (5.48) or vehicle (5.20) groups (P<.046). There was a statistically significant difference among groups in time since onset of migraines (P=0.001), with a greater mean time since onset in the vehicle (27.4 years) and 25-U BTX-A (23.4 years) groups than in the 75-U BTX-A group (16.9 years).
Elkind, 2006[7]	Double blind	Yes	Unclear	Yes (See note)	Unclear	Low	
Chankrachang*, 2011[8]*	Double blind	Yes	Unclear	Yes	Unclear	Low	ITT planned only for efficacy measures
Petri*, 2009[9]*	Double blind	Yes	Unclear	No	Yes	High	Mean age differs by groups
Mathew, 2005[10]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Silberstein, 2005[11]	Double blind	Yes	Unclear	Yes	Unclear	Low	does not provide loss at follow-up
Anand, 2006[12]	Double blind	No	Unclear	Unclear (Table not provided, but	Unclear	Medium	Concern regarding baseline severity: in text, authors

Appendix Table D10. Risk of bias in randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults (continued)

Reference	Masking	Intention to Treat Planned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias	Other Biases
				authors mentioned "Demographic characteristics of patients in both the groups were comparable".			report mean number of headache days at baseline (4 moderate to severe headache in trt group vs. 12.6 in placebo group)
Cady, 2008[13]	Double blind	No	Unclear	Yes	Unclear	Low	
Vo, 2007[14]	Double blind	No	Unclear	Yes	Unclear	Low	Primary reason for attrition is attributable due the fluidality of personnel in a major military medical setting during a time of conflict
Aurora, 2007[15]	Double blind	Yes	Unclear	No	Unclear	Medium	
Barrientos, 2003[16]	Double blind	Yes	Unclear	Yes	Unclear	Low	
Relja, 2007[17]	Double blind	Yes	Unclear	Yes	Unclear	Low	

* Trials of abobotulinumtoxin A

Appendix Table D11. Strength of evidence of decrease in migraine frequency by ≥50% with onabotulinumtoxin A

Reference	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Silberstein, 2000[6]	Medium	Yes			
Freitag, 2008[5]	Low	Yes			
Mathew, 2005[10]	Low	Yes			
Overall	Medium	Yes	Yes	No	Low

Appendix Table D12. Decrease in migraine frequency by ≥50% with onabotulinumtoxin A, pooled results from randomized controlled clinical trials, random effects models with inverse variance weights

Duration of Active Treatment in Weeks	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Weight, Inverse Variance	Absolute Risk Difference (95% CI)	Weight, Inverse Variance
12 weeks	Silberstein, 2000[6] Medium	19/42	5/21	1.9 (0.8 to 4.4)	6.88	0.21 (-0.02 to 0.45)	13.85
16 weeks	Freitag, 2008[5] Low	6/20	3/21	2.1 (0.6 to 7.3)	3.1	0.16 (-0.09 to 0.41)	12.33
24 weeks	Mathew, 2005[10] Low	94/173	69/182	1.4 (1.1 to 1.8)	90.02	0.16 (0.06 to 0.27)	73.82
12-24 weeks	Pooled	119/235	77/224	**1.5 (1.2 to 1.8)**	100	**0.17 (0.08 to 0.26)**	100
Heterogeneity test				P value=0.7 I squared=0%		P value=0.9 I squared=0%	

Bold = differences are statistically significant when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D13. Migraine headache frequency (change from baseline) with onabotulinumtoxin A, pooled results from randomized controlled clinical trials, random effects models

Reference	Dose, Weeks of Treatment	Sample in Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference	Mean Difference (95% CI)	Mean Ratio (95% CI)
Elkind, 2006[7]	7.5U 4 weeks	105 [106]	-1.5 [2.6]	-1.3 [2.4]	-0.1 (-0.3 to 0.2)	-0.2 (-0.9 to 0.5)	1.1 (0.7 to 1.8)
	7.5U 8 weeks	105 [106]	-1.6 [2.2]	-1.4 [2.3]	-0.1 (-0.3 to 0.2)	-0.2 (-0.8 to 0.4)	1.1 (0.7 to 1.7)
	7.5U 12 weeks	105 [106]	-1.4 [2.6]	-1.2 [2.6]	-0.1 (-0.3 to 0.2)	-0.1 (-0.8 to 0.6)	1.1 (0.6 to 1.9)
	7.5U 16 weeks	105 [106]	-1.5 [2.6]	-1.5 [2.4]	0.0 (-0.3 to 0.3)	0.0 (-0.7 to 0.7)	1.0 (0.6 to 1.6)
	25U 4 weeks	101 [106]	-1.4 [2.2]	-1.3 [2.4]	0.0 (-0.3 to 0.3)	0.0 (-0.7 to 0.6)	1.0 (0.6 to 1.6)
	25U 8 weeks	101 [106]	-1.4 [2.7]	-1.4 [2.3]	0.0 (-0.2 to 0.3)	0.1 (-0.6 to 0.7)	1.0 (0.6 to 1.6)
	25U 12 weeks	101 [106]	-1.3 [2.6]	-1.2 [2.6]	0.0 (-0.3 to 0.2)	-0.1 (-0.8 to 0.6)	1.1 (0.6 to 1.9)
	25U 16 weeks	101 [106]	-1.0 [2.7]	-1.5 [2.4]	0.2 (-0.1 to 0.5)	0.5 (-0.2 to 1.2)	0.7 (0.4 to 1.2)
	50U 4 weeks	106.0 [106]	-1.1 [2.2]	-1.3 [2.4]	0.1 (-0.2 to 0.4)	0.2 (-0.4 to 0.8)	0.8 (0.5 to 1.4)
	50U 8 weeks	106.0 [106]	-1.2 [2.4]	-1.4 [2.3]	0.1 (-0.1 to 0.4)	0.3 (-0.3 to 0.9)	0.8 (0.5 to 1.3)
	50U 12 weeks	106.0 [106]	-1.4 [2.3]	-1.2 [2.6]	-0.1 (-0.3 to 0.2)	-0.1 (-0.8 to 0.5)	1.1 (0.7 to 1.9)
	50U 16 weeks	106.0 [106]	-1.6 [2.5]	-1.5 [2.4]	0.0 (-0.3 to 0.2)	-0.1 (-0.7 to 0.6)	1.0 (0.7 to 1.6)
Chankrachang*, 2011[8]*	240U 12 (one time injection) weeks	43.0 [21]	1.8 [3.2]	2.2 [2.6]	-0.1 (-0.7 to 0.4)	-0.4 (-1.9 to 1.1)	0.8 (0.4 to 1.7)
	120U 12 (one time injection) weeks	43.0 [21]	2.0 [2.4]	2.2 [2.6]	-0.1 (-0.6 to 0.4)	-0.3 (-1.6 to 1.0)	0.9 (0.5 to 1.6)
Pooled					0.0 (-0.1 to 0.1)	0.0 (-0.2 to 0.2)	-0.02 (-0.15 to 0.12)

* trials of abobotulinumtoxin A

Appendix Table D14. Severity, disability, and quality of life with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials)

Definition	Reference	Dose, Weeks of Treatment	Sample Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	P value	Mean Difference (95% CI)
Migraine Disability Assessment Scores (MIDAS)	Freitag, 2008[5]	100U 16weeks	20.0 [21]	51.0 [0.0]	63.0 [0.0]		0.445	
Headache Pain Specific QoL (no information on scale)	Freitag, 2008[5]	100U 16weeks	20.0 [21]	178.0 [0.0]	191.0 [0.0]		0.078	
Change in Migraine Disability Assessment (MIDAS) from baseline	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-21.6 [38.7]**	**4.8 [18.9]**	**-0.8 (-1.3 to -0.2)**		**-26.4 (-41.1 to -11.7)**
Change in Migraine Impact Questionnaire (MIQ): Global assessment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**2.0 [1.4]**	**0.9 [1.5]**	**0.8 (0.2 to 1.3)**		**1.1 (0.3 to 1.9)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of non-Rx treatment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.1 [1.2]**	**-0.3 [1.5]**	**1.1 (0.5 to 1.7)**		**1.5 (0.7 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of Rx treatment	Cady, 2008[13]	139 U 12 (one time injection)weeks	40.0 [19]	0.5 [1.6]	0.4 [1.4]	0.0 (-0.5 to 0.6)		0.1 (-0.7 to 0.9)
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of current Treatment on frequency of migraine symptoms	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.4 [1.7]**	**0.0 [1.3]**	**0.9 (0.3 to 1.4)**		**1.4 (0.6 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Effectiveness of current Treatment on severity of migraine symptoms	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.5 [1.8]**	**0.1 [1.4]**	**0.9 (0.3 to 1.4)**		**1.4 (0.6 to 2.2)**
Change in Migraine Impact Questionnaire (MIQ): Feelings with current preventive migraine treatment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.7 [1.9]**	**0.4 [1.9]**	**0.7 (0.1 to 1.3)**		**1.3 (0.3 to 2.3)**

Appendix Table D14. Severity, disability, and quality of life with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of Treatment	Sample Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	P value	Mean Difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ): Side effects of current preventive migraine treatment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.7 [1.8]**	**0.5 [1.6]**	**0.7 (0.1 to 1.3)**		**1.2 (0.3 to 2.1)**
Change in Migraine Impact Questionnaire (MIQ): Number of doses required for migraine preventive treatment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.3 [2.0]**	**-0.2 [1.7]**	**0.8 (0.2 to 1.3)**		**1.4 (0.5 to 2.4)**
Change in Migraine Impact Questionnaire (MIQ): Overall effectiveness of current migraine preventive treatment	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.4 [2.1]**	**0.1 [0.9]**	**0.7 (0.2 to 1.3)**		**1.3 (0.5 to 2.1)**
Change in Migraine Impact Questionnaire (MIQ): Ability to self-manage migraine symptoms	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**1.0 [1.3]**	**-0.1 [1.3]**	**0.8 (0.3 to 1.4)**		**1.1 (0.4 to 1.8)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.5 [1.2]	-0.2 [1.1]	-0.3 (-0.8 to 0.3)		-0.3 (-1.0 to 0.3)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.8 [1.2]	-0.3 [1.1]	-0.4 (-1.0 to 0.1)		-0.5 (-1.1 to 0.1)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Mood	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.1 [1.2]**	**-0.4 [0.9]**	**-0.7 (-1.2 to -0.1)**		**-0.7 (-1.3 to -0.2)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	Cady, 2008[13]	139 U 12 (one time injection)weeks	40.0 [19]	-0.5 [1.1]	-0.1 [1.1]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	**Cady, 208[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.7 [1.1]**	**0.1 [0.9]**	**-0.8 (-1.3 to -0.2)**		**-0.8 (-1.3 to -0.2)**

Appendix Table D14. Severity, disability, and quality of life with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of Treatment	Sample Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	P value	Mean Difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Ability to walk or move about	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.6 [1.1]**	**0.2 [0.8]**	**-0.8 (-1.3 to -0.2)**		**-0.8 (-1.3 to -0.3)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.3]	-0.4 [0.8]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.8 [1.1]**	**-0.1 [1.2]**	**-0.6 (-1.2 to -0.1)**		**-0.7 (-1.3 to -0.1)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Sleep	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.8 [1.0]**	**-0.2 [0.8]**	**-0.6 (-1.2 to -0.1)**		**-0.6 (-1.1 to -0.1)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.1]	-0.4 [0.9]	-0.4 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.9 [1.1]**	**-0.1 [0.9]**	**-0.7 (-1.3 to -0.1)**		**-0.8 (-1.3 to -0.2)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Normal work	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.1 [1.0]**	**-0.3 [0.8]**	**-0.8 (-1.4 to -0.2)**		**-0.8 (-1.3 to -0.3)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.5 [1.1]	0.1 [0.9]	-0.6 (-1.1 to 0.0)		-0.6 (-1.1 to -0.1)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.6 [1.0]**	**0.3 [1.0]**	**-0.9 (-1.5 to -0.3)**		**-0.9 (-1.5 to -0.4)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Recreational activity	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-0.9 [1.0]**	**0.2 [1.2]**	**-1.0 (-1.6 to -0.4)**		**-1.1 (-1.7 to -0.5)**
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.6 [1.2]	-0.2 [1.0]	-0.3 (-0.9 to 0.2)		-0.4 (-0.9 to 0.2)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	Cady, 2008[13]	139 U 12 (one time injection) weeks	40.0 [19]	-0.7 [1.3]	0.0 [1.1]	-0.6 (-1.1 to 0.0)		-0.7 (-1.3 to 0.0)

Appendix Table D14. Severity, disability, and quality of life with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of Treatment	Sample Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	P value	Mean Difference (95% CI)
Change in Migraine Impact Questionnaire (MIQ)-QOL: Enjoyment of life	**Cady, 2008[13]**	**139 U 12 (one time injection) weeks**	**40.0 [19]**	**-1.0 [1.1]**	**-0.2 [1.1]**	**-0.7 (-1.3 to -0.1)**		**-0.8 (-1.3 to -0.2)**
Beck's Depression Inventory (BDI)	Petri*, 2009[9]	210U 12 (one time injection) weeks	32.0 [32]				No differences	
Beck's Depression Inventory (BDI)	Petri*, 2009[9]	80U 12 (one time injection) weeks	32.0 [32]				No differences	
Change from baseline in total Headache Impact Test-6 (HIT-6) score	**Aurora, 2010[1]**	**155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks**	**341.0 [338]**	**-4.7 [0.0]**	**-2.4 [0.0]**		**<.001**	
Change from baseline in total Headache Impact Test-6 (HIT-6) score	**Diener, 2010[2]**	**155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks**	**347.0 [358]**	**-4.9 [-2.4]**			**<.001**	
Severity of headache (VAS 10-point, 10 indicate no pain)	**Anand, 2006[12]**	**50U 12 (one treatment) weeks**	**16.0 [16]**	**7.3 [3.0]**	**2.6 [1.0]**	**2.1 (1.2 to 3.0)**		**4.7 (3.1 to 6.2)**
Severity of headache (VAS 10-point, 10 indicate no pain)	**Anand, 2006[12]**	**50U 12 (one treatment) weeks**	**16.0 [16]**	**7.6 [3.2]**	**2.7 [1.1]**	**2.1 (1.2 to 2.9)**		**4.9 (3.2 to 6.5)**
Severity of pain	Vo, 2007[14]	Differs by weight: 1) < 65 kg: 135 U; 2) ≥ 65 kg: 205 U GLM Repeated measure analysis of variance during 12 weeks	15.0 [17]				Not significant	

Appendix Table D14. Severity, disability, and quality of life with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition	Reference	Dose, Weeks of Treatment	Sample Active [Control]	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	P value	Mean Difference (95% CI)
Mean severity of migraines (change from baseline)	**Silberstein, 2000[6]**	**25U**	**42.0 [21]**				**Significantly greater reduction in the 25U group than in the vehicle group at week 4 & week 8 (≤0.029).**	
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	240U 12 (one time injection) weeks	43.0 [21]	-14.6 [74.3]	-10.5 [22.8]	-0.1 (-0.6 to 0.5)		-4.1 (-28.3 to 20.2)
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	240U 12 (one time injection) weeks	43.0 [21]	-11.3 [85.5]	-5.2 [39.3]	-0.1 (-0.6 to 0.4)		-6.1 (-36.7 to 24.5)
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	240U 12 (one time injection) weeks	43.0 [21]	-22.3 [83.4]	-9.7 [53.0]	-0.2 (-0.7 to 0.4)		-12.5 (-46.2 to 21.2)
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	120U 12 (one time injection) weeks	43.0 [21]	-14.9 [35.9]	-10.5 [22.8]	-0.1 (-0.7 to 0.4)		-4.4 (-18.9 to 10.1)
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	120U 12 (one time injection) weeks	43.0 [21]	-10.7 [49.9]	-5.2 [39.3]	-0.1 (-0.6 to 0.4)		-5.5 (-27.9 to 17.0)
Change in the mean total intensity score (no details) from baseline	Chankrachang*, 2011[8]*	120U 12 (one time injection) weeks	43.0 [21]	-16.1 [32.5]	-9.7 [53.0]	-0.2 (-0.7 to 0.4)		-6.4 (-31.0 to 18.2)

Bold = differences are statistically significant when 95% CI of mean difference estimates do not include 0
CI = confidence interval
* trials of abobotulinumtoxin A

Appendix Table D15. Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	Country	Design	Total Sample [Number Analyzed] % Women	Age of Subjects (Mean or Median)	Definition of Migraine	Presence of Aura	Duration of Migraine	Headache Frequency at Baseline/ Month	Concomitant Treatments
Storey, 2001[18]	Not reported	Randomized controlled clinical trial	40 [Not reported] 97.5% female	Mean 38.2 years	International Headache Society (IHS) criteria	Not reported	Not reported	4.7	Not reported
Edwards, 2003[19]	Previously reported	Randomized controlled clinical trial	70 [70] 97.1% female	Mean 41.1 years	International Headache Society criteria	Not reported	Not reported	4.5	Not reported
Silvestrini, 2003[20]	Italy	Randomized controlled clinical trial	28 [28] 64.3% female	Mean 43.5 years	International Headache Society criteria	All patients had a history of migraine without aura attacks as inclusion criterion	3 years	20	Not reported
Silberstein, 2003[21]	Not reported	Randomized controlled clinical trial	469 [Not reported] % females not reported	Not reported	International Headache Society criteria	Not reported	At least 6 months	2 to 12	Not reported
Brandes, 2004[22]	North America	Randomized controlled clinical trial	483 [468] 86.8% female	Mean 38.9 years	International Headache Society (IHS) criteria	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2004[23]	USA	Randomized controlled clinical trial	487 [469] 89.1% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2004[24]	Italy	Randomized controlled clinical trial	115 [72] 54.2% female	Mean 39.2 years	International Headache Society (1988) criteria	Patients with migraine without aura, n (%): Topiramate: 27 (77), Placebo: 31 (84)	Not reported	5.5	Subjects on continuing medication for other pathologies were included and did not modify the dosages during the study

Appendix Table 15 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total Sample [Number Analyzed] % Women	Age of Subjects (Mean or Median)	Definition of Migraine	Presence of Aura	Duration of Migraine	Headache Frequency at Baseline/ Month	Concomitant Treatments
Bussone, 2005[25]	Not reported	Randomized controlled clinical trial (Pooled analysis)	758 [756] 84.3% female	Mean 39.8 years	International Headache Society criteria	Not reported	Not reported	5.4	Not reported
Diamond, 2005[26]	Not reported	Randomized controlled clinical trial	756 [756] 84.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	3 to 12	Not reported
Silberstein, 2006[27]	USA	Randomized controlled clinical trial	469 [469] 88.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2006[28]	Italy	Randomized controlled clinical trial	50 [35] 68.6% female	Mean 45.9 years	International Classification of Headache Disorders 2nd Edition	Not reported	4.97 years	Not reported	Not reported
Silberstein, 2006[29]	USA	Randomized controlled clinical trial	213 [Variable] 85.8% female	Mean 40.5 years	International Headache Society criteria	75 subjects had migraine with aura	Not reported	4.9	Not reported
Brandes, 2006[30]	USA	Randomized controlled clinical trial	483 [468] 86.8% female	Mean 38.9 years	International Headache Society criteria for migraine with or without aura	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2007[31]	USA	Randomized controlled clinical trial	328 [Variable] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration: 9.2 years; Age at onset: 19.7 years	Not reported	Not reported
Lofland, 2007[32]	North America	Randomized controlled clinical trial	325 [325] 89.0% female	Mean 40 years	International Headache Society criteria	Not reported	Not reported	3 to 12	Not reported
Limmroth, 2007[33]	Not reported	Randomized controlled clinical trial	756 [756] 84.0% female	Mean 40 years	International Headache Society criteria	Not reported	Not reported	7.3	Not reported
Diener, 2007[34]	Not reported	Randomized controlled clinical trial	59 [59] 74.5% female	Mean 46 years	Second edition of The International	Not reported	At least 1 year	Not reported	Not reported

Appendix Table 15 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total Sample [Number Analyzed] % Women	Age of Subjects (Mean or Median)	Definition of Migraine	Presence of Aura	Duration of Migraine	Headache Frequency at Baseline/ Month	Concomitant Treatments
					Classification of Headache Disorders criteria				
Lainez, 2007[35]	Not reported	Randomized controlled clinical trial	774 [758] 84.4% female	Mean 39.9 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported
Freitag, 2007[36]	USA	Randomized controlled clinical trial (Pooled analysis)	937 [937] 87.7% female	Mean 39.7 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Dahlof, 2007[37]	Not reported	Randomized controlled clinical trial	756 [756] 84.3% female	Mean 39.8 years	Not reported	Not reported	Not reported	3 to 12	Not reported
Diener, 2007[38]	21 countries in Europe	Randomized controlled clinical trial	818 [Not reported] 89.0% female	Mean 40·1 years	International Headache Society criteria	Not reported	Not reported	8.7	Not reported
Dodick, 2007[39]	USA	Randomized controlled clinical trial	328 [306] 85.3% female	Mean 38.2 years	International Classification of Headache Disorders, 2nd edition. However, for the inclusion criterion chronic migraine was defined by Silberstein–Lipton criteria	Not reported	Age at onset: 19.7 years	Not reported	Not reported
Adelman, 2008[40]	USA, Australia, Canada, Denmark, Finland, France, Germany, Italy, Korea,	Randomized controlled clinical trial	1580 [1580] 85.0% female	Mean 40.1 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported

Appendix Table 15 Randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Country	Design	Total Sample [Number Analyzed] % Women	Age of Subjects (Mean or Median)	Definition of Migraine	Presence of Aura	Duration of Migraine	Headache Frequency at Baseline/ Month	Concomitant Treatments
	the Netherlands, South Africa, Spain, Sweden, Taiwan, and the United Kingdom								
Silberstein, 2009[41]	USA	Randomized controlled clinical trial	328 [321] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration: 9.2 years; Age at onset: 19.7 years	Not reported	Not reported
Lipton, 2011[42]	Not reported	Randomized controlled clinical trial	385 [Variable] 10.9% female	Mean 40.3 years	International Headache Society criteria 1.1,1.2	Not reported	Age at migraine onset: 20.3 years	Not reported	Not reported

Appendix Table D16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
Storey, 2001[18]	Industry	Yes	Yes	Not reported	Not applicable
Edwards, 2003[19]	Industry	Yes	Yes	Yes	Ms. Potter is on the Speakers' Bureau for biogen, GlaxoSmithKline and Ortho-McNeil Pharmaceutical, Inc, and has received funding from Biogen, Ortho-McNeil Pharmaceutical, Inc, Pfizer Inc, Wyeth Pharmaceuticals for previous research
Silvestrini, 2003[20]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2003[21]	Not reported	Not reported	Not reported	Not reported	Not applicable
Brandes, 2004[22]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, Allergan, UCB Pharma, Johnson & Johnson, AstraZeneca, Pfizer, Bristol Myers-Squibb, Winston Laboratories, Forest Laboratories, Sanofi-Synthelabo, and Elan Pharmaceuticals; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Merck, Allergan, Pfizer, Pharmacia, Ortho-McNeil, and UCB Pharma; has served as a consultant to Merck, GlaxoSmithKline, Pfizer, AstraZeneca, Allergan, and Ortho-McNeil; and has received educational funding from GlaxoSmithKline. Dr Saper has received research grants from GlaxoSmithKline, AstraZeneca, Merck, Abbott, Allergan, Elan, Pfizer, Ortho-McNeil, and Novartis; has served on advisory boards or as a consultant for AstraZeneca, GlaxoSmithKline, Allergan, Ortho-McNeil, and Medtronic; and has served on the speakers bureau for GlaxoSmithKline, Merck, AstraZeneca, Ortho-McNeil, Pfizer, and Xcel. Dr Diamond has served as a speaker, consultant, or both or has conducted research for AstraZeneca, Bristol-Myers Squibb, Ortho- McNeil, Elan, GlaxoSmithKline, Merck, and Pfizer. Dr Couch has participated in research for, been an advisory board member of, and served as a speaker for Ortho-McNeil.
Silberstein, 2004[23]	Industry	Yes	Yes	Yes	Dr. Silberstein is on the advisory panel of, speakers bureau of, or serves as a consultant for Abbott Laboratories, Allergan, Inc, AstraZeneca, Elan Pharmaceutical Research Corp, Eli Lilly, Ortho-

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					McNeil Pharmaceutical, Merck & Co, and GlaxoSmithKline; receives research support from Allergan, Inc, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Merck & Co, Ortho-McNeil Pharmaceutical, Pfizer, Inc, UCB Pharma, and Vernalis; and has received educational grants from Abbott Laboratories, Allergan, Inc, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck & Co, Ortho-McNeil Pharmaceutical, and Parke-Davis. Drs Neto and Jacobs and Ms Schmitt hold shares in Johnson & Johnson Pharmaceutical Research and Development, LLC, a subsidiary of Johnson & Johnson Corporation.
Mei, 2004[24]	Not reported	Yes	Yes	Not reported	Not applicable
Bussone, 2005[25]	Not reported	Yes	Yes	Not reported	Not applicable
Diamond, 2005[26]	Industry	Yes	Yes	Not reported, however, George Papadopoulos is from Jonhson & Johnson Pharmaceutical Services, LLC, Raritan, NJ; Dr. Neto is from Johnson & Johnson Pharmaceutical Research & Development, LLC, Raritan, NJ; and Dr. Wu is from Ortho-McNeil Neurologies, Inc., Raritan, NJ	
Silberstein, 2006[27]	Industry	Yes	Yes	Yes	George Papadopoulos is from Johnson and Johnson Pharmaceutical Services, LLC, Raritan, NJ, USA and Steven Greenberg from Ortho-McNeil Neurologies, Titusville, NJ, USA. Personnel of Pharmaceutical Research and Development , Ortho-McNeil Neurologics, Inc, Titusville, New Jersey, and Phase Five Communications, New York, New York, contributed to the preparation of the manuscript
Mei, 2006[28]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[29]	Industry	Yes	Yes	Not reported	Not applicable

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
Brandes, 2006[30]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck & Co, Inc, GlaxoSmithKline, UCB Pharma, Allergan Inc, Johnson & Johnson, Astra-Zeneca Pharmaceuticals LP, Pfizer Inc, Bristol-Meyers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Inc, Novartis, Endo Pharmaceuticals, Pozen, Vernalis, Ortho-McNeil, and Advanced Bionics; has served on the speaker's bureau for GlaxoSmith-Kline, AstraZeneca Pharmaceuticals LP, Pfizer Inc, Merck & Co, Inc, Ortho-McNeil, Allergan Inc, MedPointe Pharmaceuticals, Endo Pharmaceuticals, UCB Pharma; has served as a consultant to Merck & Co, Inc, GlaxoSmithKline, Pfizer Inc, AstraZeneca Pharmaceuticals LP, Allergan Inc, Ortho-McNeil, and Aradigm Corp; and has received an educational grant from GlaxoSmithKline. Dr Kudrow has been on a speaker's bureau of GlaxoSmithKline and Ortho-McNeil and has received grant and research support from Ortho-McNeil, GlaxoSmithKline, Pozen, Merck & Co, Inc, and Eisai Inc. Dr Fairclough received financial support as a consultant to perform analyses of the data in this study. Drs Rupnow and Greenberg are fulltime employees of Johnson & Johnson. Dr Rothrock has served as a paid consultant to Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pozen, and Allergan Inc; has received research support from those companies and from Abbott Laboratories, Elan Corporation, Esai Inc, and AstraZeneca Pharmaceuticals LP; and has received honoraria for lecturing from Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Elan Corporation, and Endo Pharmaceuticals.
Silberstein, 2007[31]	Industry	Yes	Yes	Yes	Dr. Silberstein has received personal compensation for activities with: GlaxoSmith-Kline, Inc., Johnson & Johnson, Merck & Co., Inc., UCB Pharma, AstraZeneca Pharmaceuticals, Inc., Pfizer, Inc., Allergan, Inc., Pozen, Inc., Abbott Laboratories, Inc., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					capacity for CurrentPain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Inc., Johnson & Johnson, Merck&Co., Inc., Pfizer, Inc., Allergan, Inc., and Abbott Laboratories, Inc. Dr. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan,Inc., Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil, Pfizer, Pozen, among other companies. Dr. Dodick has received personal compensation for activities with Allergan, Inc., GlaxoSmith-Kline, Inc., Pfizer, Inc., Endo Pharmaceuticals, Ortho-McNeil Pharmaceutical, Inc., Merck & Co., Inc., Medtronic, Neuralieve; has received personal compensation in an editorial capacity for Headache Currents; and has received research support from St. Jude, Allergan, Inc., Medtronic, Inc., National Institutes of Health, Mayo Clinic College of Medicine, and Advanced Bionics. Dr. Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer, Inc., and GlaxoSmithKline, Inc., and has received research support from Alzyer, AstraZeneca Pharmaceuticals, Inc., GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Precision, Division of Boston Scientific, Solvay S.A., and Vernalis. Dr. Ramadan has received personal compensation for activities with GlaxoSmithKline, Inc., Ortho- McNeil Neurologics, Inc., Eli Lilly & Company, Eisai, Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Pfizer, Inc., Merck & Co., Inc., Aradign Corp., Boehringer Ingelheim Pharmaceuticals and Map Pharmaceuticals; has received personal compensation in an editorial capacity for Web Alert; and has received research support from Ortho-McNeil Neurologics, Eli Lilly&Company, Pfizer, Inc., and the National Headache Ambassador Program. Dr. Mathew has received personal compensation for

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					activities with Eisai. Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, UCB Pharma, Allergan, Johnson & Johnson, AstraZeneca, Pfizer, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Novartis, Endo, Pozen, Inc., Vernalis, Ortho-McNeil, Advanced Bionics; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Pfizer, Merck, Ortho-McNeil, Allergan, MedPointe Pharmaceuticals, Endo, UCB Pharma; has served as a consultant to Merck, GlaxoSmith-Kline, Pfizer, AstraZeneca, Allergan, Ortho-McNeil, Aradigm Corporation; and has received educational funding from GlaxoSmithKline. Dr. Bigal has received personal compensation for activities from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, UCB, AstraZeneca, Pfizer, Inc., and Advance PCS and has received research support from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, Pfizer, UCB, AstraZeneca, and Advance PCS. Dr. Saper has received honoraria for speaking from GlaxoSmithKline, Merck & Co., Inc., Abbott Laboratories, Inc., Elan Corporation, AstraZeneca Pharmaceuticals, Pfizer, Inc., Ortho-McNeil Pharmaceuticals, Bristol-Myers Squibb, Medtronic, Inc., Endo Pharmaceuticals, Advanced Bionics, Pozen, Inc., and Penwest Pharmaceuticals Co; has received personal compensation in an editorial capacity for Pain Watch and Migraine Monitor; holds stock in Pozen, Inc.; and has received research support from Novartis, Ortho-McNeil Pharmaceuticals, Merck & Co., Inc., GlaxoSmithKline, Allergan, Inc., Eisai, Inc., AstraZeneca Pharmaceuticals, Abbott, Advanced Bionics, Medtronic, Renovis, and Pozen, Inc. Dr. Ascher is an employee of Ortho-McNeil Janssen Scientific Affairs, LLC. Dr. Jordan is an employee of PriCara, a Unit of Ortho-McNeil, Inc. Drs. Greenberg and Joseph Hulihan are employees of Ortho-McNeil Neurologics.

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
Lofland, 2007[32]	Industry	Yes	Yes	Yes	Jennifer H. Lofland received grant from Ortho-McNeil Janssen, Inc
Limmroth, 2007[33]	Industry	Yes	Yes	Yes	Volker Limmroth received honoraria as speaker from Janssen-Cilag, Germany. Susanne Schwalen is an employee of Janssen-Cilag, Germany
Diener, 2007[34]	Industry	Not reported	Not reported	Yes	JC Van Oene, M Lahaye and S Schwalen are employees of Janssen-Cilag
Lainez, 2007[35]	Not reported	Yes	Yes	Yes	Miguel JA La´ inez has received personal compensation or research support from activities with Allergan, Inc., Almirall SA, GlaxoSmithKline, Inc Jansen Cilag, Inc., Menarini, Merck & Co., Inc, Medtronic and Pfizer Inc. Frederick Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals,., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer Inc, and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Advanced Bionics, Solvay S.A., and Vernalis. Joop Pfeil is a paid consultant for Janssen Pharmaceutical/J & J, Novartis, Sanofi-Aventis, Pfizer, Schering-Plough, Numico, Vitatron, Actelion Pharmaceuticals and Sankyo. S. Ascher is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. W.H. Olson is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. S. Schwalen is a full-time employee of Janssen-Cilag GmbH.
Freitag, 2007[36]	Industry	Yes	Yes	Yes	Dr. Freitag has received honoraria, consulting fees, and research grant funds in excess of $10,000 per year from Johnson & Johnson and Ortho-McNeil Neurologics. Dr. Forde has received honoraria in excess of $10,000 per year from Johnson & Johnson and Ortho-McNeil Neurologics. Drs. Neto and Wang and Ms Schmitt are paid employees of Johnson & Johnson. Drs. Wu and Hulihan are paid employees of Ortho-McNeil Neurologics.
Dahlof, 2007[37]	Industry	Yes	Yes	Yes	Professor Carl Dahlöf has been a consultant/scientific advisor on advisory boards, clinical trials, and

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					investigator-initiated trials and a speaker for: Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Janssen Cilag, Merck, Lilly, NMT Medical Inc., Novartis, Ortho-McNeil Pharmaceutical, Pharmacia, Pfizer, Pierre Fabre, and St Jude Medical EMEAC. Elizabeth Loder has had no financial relationship with any pharmaceutical company since July 2006, except grant support from NMT for a clinical trial. She has been a speaker, received grant support, or been a consultant for: OrthoMcNeil, Endo, AstraZeneca, GlaxoSmithKline, Pfizer, and Allergan. She serves on the Board of Directors of the American Headache Society, the Executive Council of the International Headache Society, and the Board of the Headache Cooperative of New England. Merle Diamond has served as a consultant and/or conducted research with AstraZeneca, Ortho-McNeil Neurologies, GlaxoSmithKline, Merck and Co., Pfizer, and Primary Care Network. Marcia Rupnow is a full-time salary employee of Ortho-McNeil Janssen Scientific Affairs, LLC. George Papadopoulos was an employee of J&J Pharmaceutical Services at the time of study completion. Lian Mao is a full-time salary employee of Ortho-McNeil Janssen Scientific Affairs, LLC.
Diener, 2007[38]	Industry	Yes	Yes	Yes	Hans-Christoph Diener, Reto Agosti, Gianni Allais, Gennaro Bussone, Brendan Davies, Michel Lanteri-Minet, Mustafa Ertas, Uwe Reuter, Margarita Sanchez Del Rio, and Jean Schoenen have participated in clinical trials and advisory boards for Janssen-Cilag. Paul Bergmans, Susanne Schwalen, Joop van Oene are employees of Janssen-Cilag EMEA (Europe, Middle East, and Africa). Hans -Chirstoph Diener has received honoraria from Addex Pharmaceuticals, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid Pharmaceuticals, Böhringer Ingelheim, Bristol-Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Eli Lilly, F Hoffmann-La Roche, 3M Medica, Merck Sharp and Dohme, Novartis Pharmaceuticals, Johnson and Johnson,

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					Pierre Fabre, Pfizer, Schaper and Brümmer, Sanofi - Aventis, and Weber and Weber, and financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer.
Dodick, 2007[39]	Industry	Yes	Yes	Yes	David W. Dodick is a consultant/advisor for Eli Lilly, Glaxo-SmithKline, Merck, Neuralieve, Ortho-McNeil. He is involved in research studies with Advanced Bionics, AstraZeneca, Medtronic, and Alexza, for which his academic institution has received research grants. He is also the principal investigator of a multicenter clinical trial with St. Jude. He has no stock or equity in any pharmaceutical company. Stephen Silberstein has received personal compensation for activities with GlaxoSmithKline, Inc.; Johnson & Johnson; Merck & Co., Inc.; UCB Pharma; AstraZeneca Pharmaceuticals; Pfizer Inc.; Allergan, Inc.; Pozen, Inc.; Abbott Laboratories, Inc.; Eli Lilly & Company; NPS; and Xcel Pharmaceuticals. Dr. Silberstein has received personal compensation in an editorial capacity for Current Pain and Headache. Dr. Silberstein has received financial support for scholarly activities from GlaxoSmithKline, Inc.; Johnson & Johnson; Merck & Co., Inc.; Pfizer Inc.; Allergan, Inc.; and Abbott Laboratories, Inc. Joel Saper has received honoraria for speaking from Glaxo-SmithKline; Merck & Co., Inc.; Abbott Laboratories, Inc.; Elan Corporation; AstraZeneca Pharmaceuticals; Pfizer Inc.; Ortho-McNeil Pharmaceuticals, Inc.; Bristol-Myers Squibb; Medtronic Inc.; Endo Pharmaceuticals; Advanced Bionics; Pozen, Inc.; and Penwest Pharmaceuticals Co. Dr. Saper has received personal compensation in an editorial capacity for PainWatch and Migraine Monitor. He holds stock in Pozen, Inc. and has received research support from Novartis; Ortho-McNeil Pharmaceuticals, Inc; Merck & Co., Inc.; GlaxoSmith-Kline; Allergan, Inc.; Eisai Inc.; AstraZeneca Pharmaceuticals; Abbott; Advanced Bionics; Medtronic; Renovis; and Pozen,Inc. Fred G. Freitag has received personal compensation for

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					activities with Allergan, Inc.; AstraZeneca Pharmaceuticals; Merck & Co., Inc.; Ortho-McNeil Pharmaceuticals, Inc.; Valeant Pharmaceuticals International; Pfizer Inc.; and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer; AstraZeneca Pharmaceuticals; GlaxoSmithKline, Inc.; Merck & Co., Inc.; Ortho-McNeil Pharmaceuticals, Inc.; Advanced Bionics; Solvay S.A.; and Vernalis. Roger K. Cady has received personal compensation for activities with Allergan; Atrix Labs; Capnia; Endo; GlaxoSmith-Kline; Johnson & Johnson; Med Point; Merck; Ortho-McNeil Pharmaceuticals, Inc.; and Winston Labs. Dr. Cady received compensation from NIPC for serving as a co-editor of their migraine newsletter. Dr. Cady has received research support from Abbott; Allergan; Alexa; Aradigm Corp; Capnia; Cipher; Eisai Pharmaceuticals; Endo Pharmaceuticals; GelStat; Glaxo-SmithKline; Johnson & Johnson; Matrixx; Merck; Ortho-McNeil Pharmaceuticals, Inc.; Pfizer Inc.; and Vernalis. Alan M. Rapoport has received personal compensation from the following pharmaceutical companies, advisory boards, speaker's bureau, research or educational grants: Abbott Laboratories; Allergan, Inc.; AstraZeneca; Eisai Pharmaceuticals; Endo Pharmaceuticals; Forest Laboratories; GlaxoSmithKline; Endo Pharmaceuticals; Forest Laboratories; GlaxoSmithKline; Merck; Ortho-McNeil Pharmaceuticals, Inc.; Pfizer Inc.; UCB Pharma; Valeant; Vernalis ; and Winston. Ninan T. Mathew has received personal compensation for activities with Eisai Pharmaceuticals. Joseph Hulihan, Concetta Crivera, Marcia F.T. Rupnow, Lian Mao, Gary Finlayson, and Steven J. Greenberg are employees of Ortho-McNeil Janssen Scientific Affairs, LLC.
Adelman, 2008[40]	Industry	Yes	Yes	Yes	James Adelman: Clinical Trials 1998–2006 (Ortho-McNeil Pharmaceuticals), Advisory Boards (Ortho-McNeil Pharmaceuticals), Speaker (Ortho-McNeil Pharmaceuticals); Frederick Freitag: Consultant,

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					honoraria recipient (OrthoMcNeil Pharmaceuticals and Ortho-McNeil Neurologics), research grant recipient (Johnson and Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals, and Ortho-McNeil Neurologics); Miguel Lainez: grant/research recipient, consultant/scientific advisor, honoraria recipient (Allergan, Almirall Prodesfarma, Boehringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen Cilag, Johnson and Johnson, MSD, Novartis, Pierre Fabre, and Sanofi-Synthelabo).
Silberstein, 2009[41]	Industry	Yes	Yes	Yes	Stephen Silberstein has received personal compensation for activities with: Johnson & Johnson, GlaxoSmith-Kline, Merck, UCB Pharma, AstraZeneca, Pfizer, Allergan, Pozen, Abbott Laboratories., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial capacity for Current Pain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Allergan, and Abbott Laboratories. Richard B. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeill, Pfizer, and Pozen, among other companies. David W. Dodick has served as a consultant for GlaxoSmithKline, Merck, Allergan, Endo, Pfizer, Eli Lilly, Addex, Solvay, and Neuralieve and has received research support from Advanced Neurostimulation Systems, Medtronic, and St. Jude. Fred Freitag has received grants and research support from Advanced Bionics Corporation, Alzyer, AstraZeneca, CAPNIA, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Solvay, and Vernalis Pharmaceuticals. He has served as a consultant for Allergan, AstraZeneca, CAPNIA, Endo Pharmaceuticals, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, and Valeant Pharmaceuticals International. He has served

Appendix Table 16. Funding, ethical approval, and conflict of interest in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
					on the speaker's bureaus of AstraZeneca, GlaxoSmithKline, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Pfizer, and Valeant Pharmaceuticals International. Ninan Mathew has received personal compensation for activities involving continuing medical education and for advisory board participation from Ortho McNeil, Merck, Allergan, GlaxoSmithKline, Endo, and Valiant. Jan Brandes has received grants, research support, or served as a consultant to Merck, GlaxoSmithKline, UCB Pharma, Pfizer, Allergan, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan, Novartis, Endo, Pozen, Vernalis, Ortho-McNeil, Advanced Bionics, MedPointe, and Aradigm. Marcelo E. Bigal is a full-time employee of Merck Research Laboratories. This manuscript was written during his tenure at the Albert Einstein College of Medicine. He has received, in the past, compensation from Ortho-McNeil Pharmaceutical, AstraZeneca, GlaxoSmithKline, Merck, Allergan, MAP, NMT, and Endo, among other pharmaceutical companies. Steve Ascher, Jacqueline D. Morein, and Pamela Wright are employees of Ortho-McNeil Janssen Scientific Affairs, LLC. Steven J. Greenberg is an employee of EMD Serono Inc.
Lipton, 2011[42]	Industry	Yes	Yes	Yes	Not reported, however, David Biondi, Steven Ascher, William Olson and Joseph Hulihan were from Ortho-McNeil Janssen Scientific Affairs, USA

Appendix Table D17. Risk of bias in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication)

Reference	Masking of Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Storey, 2001[18]	Double-blind	No	Unclear	Yes (Topiramate group had no men and higher number of patients with concurrent preventative treatment, but the differences were not significant)	Unclear	Low
Edwards, 2003[19]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
Silvestrini, 2003[20]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2003[21]	Double-blind	No	Unclear	Yes	Unclear	Medium
Brandes, 2004[22]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Silberstein, 2004[23]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mei, 2004[24]	Double-blind	No	Unclear	Unclear	Unclear	Medium
Bussone, 2005[25]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diamond, 2005[26]	Double-blind	Yes	Unclear	Previously reported[22, 23, 43]	Unclear	Low
Silberstein, 2006[27]	Double-blind	Yes	Unclear	Not adequate. Topiramate 200mg/day group has lower % of women and higher % of men as compared to other groups, but the differences were not significant (previously reported)	Unclear	Medium
Mei, 2006[28]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[29]	Double-blind	Yes	Unclear	Not reported	Unclear	Medium
Brandes, 2006[30]	Double-blind	Yes	Clearly adequate	Not adequate; the % of male patients were much lower in the topiramate100mg and 200mg groups, but the difference were not significant	Unclear	Medium
Silberstein, 2007[31]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Lofland, 2007[32]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Limmroth, 2007[33]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[34]	Double-blind	Yes	Unclear	Not adequate (Mean Beck Depression Inventory scores were higher in	Unclear	Medium

Appendix Table 17. Risk of bias in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (sorted by year of publication) (continued)

Reference	Masking of Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
				placebo as compared to topiramate, but the differences were not significant)		
Lainez, 2007[35]	Double-blind	No	Unclear	Yes	Unclear	Low
Freitag, 2007[36]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Dahlof, 2007[37]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[38]	Double-blind	Yes	Unclear	Yes	Unclear	Medium
Dodick, 2007[39]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Adelman, 2008[40]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2009[41]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Lipton, 2011[42]	Double-blind	Yes	Unclear	Yes	The study mentions the significance of the outcome: ≥50% and 75% reduction in headache days and migraine headache days, however, the results are not given	Low

Appendix Table D18. Strength of evidence of migraine prevention with topiramate in adults

Outcome, Reference	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
≥50% Reduction in monthly migraine frequency[18, 20, 24, 25, 29, 31, 44]	Medium	Direct	Consistent	Precise	Moderate
≥50% Reduction in monthly migraine days[25, 34, 41]	Low	Direct	Consistent	Imprecise	Moderate
≥75% Reduction in monthly migraine days[25, 41]	Low	Direct	Consistent	Imprecise	Moderate
Complete migraine cessation[25, 29, 41]	Medium	Direct	Inconsistent	Imprecise	Low

Appendix Table D19. Migraine prevention with topiramate vs. placebo in adults (pooled results from randomized controlled clinical trials)

Outcome	Author, Year	Events/ Randomized	Events/ Randomized	Relative Risk (95% CI)	Weight Random Effects Inverse Variance	Absolute Risk Difference, (95% CI)	Weight, Random Effects Inverse Variance
Frequency:≥50% reduction	Storey, 2001[18]	5/19	2/21	2.8 (0.6 to 12.6)	3.34	0.17 (-0.07 to 0.40)	11
Frequency:≥50% reduction	Mei, 2004[24]	37/58	12/57	3.0 (1.8 to 5.2)	15.25	0.43 (0.27 to 0.59)	14.67
Frequency:≥50% reduction	Bussone, 2005[25]	188/386	93/372	1.9 (1.6 to 2.4)	27.28	0.24 (0.17 to 0.30)	19.77
Frequency:≥50% reduction	Silberstein, 2006[29]	55/140	25/73	1.1 (0.8 to 1.7)	20.61	0.05 (-0.09 to 0.19)	16.2
Frequency:≥50% reduction	Silberstein, 2007[31]	58/112	8/36	2.3 (1.2 to 4.4)	12.66	0.30 (0.13 to 0.46)	14.58
Frequency:≥50% reduction	Silvestrini, 2003[20]	10/14	1/14	10.0 (1.5 to 68.0)	2.18	0.64 (0.37 to 0.92)	9.41
Frequency:≥50% reduction	Gupta, 2007[44]	38/60	18/60	2.1 (1.4 to 3.3)	18.69	0.33 (0.17 to 0.50)	14.36
Frequency:≥50% reduction	**Pooled**	**391/789**	**159/633**	**2.0 (1.5 to 2.7)**	**100**	**0.29 (0.18 to 0.40)**	**100**
Reduction in headache days by ≥50%	Bussone, 2005[25]	175/386	81/372	2.1 (1.7 to 2.6)	50.32	0.24 (0.17 to 0.30)	41.85
Reduction in headache days by ≥50%	Diener, 2007[34]	7/32	0/27	12.7 (0.8 to 213.1)	3.07	0.22 (0.07 to 0.37)	24.44
Reduction in headache days by ≥50%	Silberstein, 2009[41]	64/165	50/163	1.3 (0.9 to 1.7)	46.61	0.08 (-0.02 to 0.18)	33.71
Reduction in headache days by ≥50%	**Pooled**	246/583	131/562	**1.7 (1.0 to 2.9)**	**100**	**0.18 (0.08 to 0.28)**	**100**
Reduction in headache days by ≥75%	Bussone, 2005[25]	98/386	41/372	2.3 (1.6 to 3.2)	60.07	0.14 (0.09 to 0.20)	52.98
Reduction in headache days by ≥75%	Silberstein, 2009[41]	25/165	18/163	1.4 (0.8 to 2.4)	39.93	0.04 (-0.03 to 0.11)	47.02

Appendix Table D19. Migraine prevention with topiramate vs. placebo in adults (pooled results from randomized controlled clinical trials) (continued)

Outcome	Author, Year	Events/ Randomized	Events/ Randomized	Relative Risk (95% CI)	Weight Random Effects Inverse Variance	Absolute Risk Difference, (95% CI)	Weight, Random Effects Inverse Variance
Reduction in headache days by ≥75%	**Pooled**	**123/551**	**59/535**	**1.9 (1.1 to 3.1)**	**100**	**0.10 (-0.01 to 0.20)**	**100**
Outcome	Heterogeneity statistics	Degree of freedom	P value Relative risk	I squared Relative risk		P value Absolute risk difference	I squared Absolute risk difference
Frequency:≥50% reduction		6	0.036	55.50%		0.001	73.60%
Reduction in headache days by ≥50%		2	0.012	77.20%		0.042	68.40%
Reduction in headache days by ≥75%		1	0.123	58.00%		0.026	79.70%

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D20. Reduction in migraine frequency and duration in randomized controlled clinical trials that examined efficacy of topiramate in adults

Definition of the Outcome	Reference Risk of Bias	Mean [Standard Deviation] with Drug	Daily Dose	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Mean monthly migraine days	Silberstein, 2004[23] Risk of bias Low	3.7 [3.3]	100 mg/day	5.3 [3.6]	-0.46 (-0.72 to -0.21)	-1.60 (-2.47 to -0.73)
Mean monthly migraine days	Mei, 2006[28] Risk of bias Low	3.1 [0.91]	100 mg/day	15.4 [4.38]	-4.30 (-5.32 to -3.27)	-12.22 (-14.17 to -10.27)
Mean monthly migraine days	Brandes, 2006[30] Risk of bias Medium	3.5 [3.5]	100 mg/day	4.5 [2.9]	-0.31 (-0.57 to -0.05)	-1.00 (-1.82 to -0.18)
Pooled with random effects	**Risk of bias Low**	**Low**	**100 mg/day**	Heterogeneity test: P value=0 I squared= 96.3%	**-1.47 (-2.55 to -0.39)**	**-4.83 (-9.44 to -0.21)**
Mean monthly migraine days	Silvestrini, 2003[20] Risk of bias Low	8.1 [8.3]	50mg/day	20.6 [4.4]	-1.9 (-2.8 to -1.0)	-12.5 (-17.4 to -7.6)
Mean monthly migraine days	Silberstein, 2004[23] Risk of bias Low	4.8 [4]	50mg/day	5.3 [3.6]	-0.1 (-0.4 to 0.1)	-0.5 (-1.5 to 0.5)
Pooled with random effects	Risk of bias Low	Low	50mg/day	Heterogeneity test: P value=0 I squared= 92.6%	-1.0 (-2.7 to 0.8)	-6.2 (-18.5 to 5.5)
Mean reduction in the monthly number of migraine days	Brandes, 2004[22] Risk of bias Low	-2.6 [3.4]	100 mg/day	-1.3 [3.5]	-0.4 (-0.6 to -0.1)	-1.3 (-2.2 to -0.4)
Mean reduction in the monthly number of migraine days	Silberstein, 2007[31] Risk of bias Low	-6.4 [5.8]	100 mg/day	-4.7 [6.1]	-0.3 (-0.5 to -0.1)	-1.7 (-3.0 to -0.4)
Mean reduction in the monthly number of migraine days	Lipton, 2011[42] Risk of bias Low	-6.6 [3.5]	100 mg/day	-5.3 [3.6]	-0.4 (-0.6 to -0.2)	-1.3 (-2.0 to -0.6)
Mean reduction in the monthly number of migraine days	Brandes, 2004[22] Risk of bias Low	-2.9 [3.41]	200mg/day	-1.3 [3.51]	-0.5 (-0.7 to -0.2)	-1.6 (-2.5 to -0.7)
Pooled with random effects	**Risk of bias Low**	**Low**	**50 to 200mg/day**	Heterogeneity test: P value=0.7 I squared= 0%	**-0.4 (-0.5 to -0.3)**	**-1.4 (-1.9 to -1.8)**
Monthly migraine frequency	Silberstein, 2004[23] Risk of bias Low	4.1 [3.6]	50mg/day	4.6 [3]	-0.2 (-0.4 to 0.1)	-0.5 (-1.3 to 0.3)

Appendix Table D20. Reduction in migraine frequency and duration in randomized controlled clinical trials that examined efficacy of topiramate in adults (continued)

Definition of the Outcome	Reference Risk of Bias	Mean [Standard Deviation] with Drug	Daily Dose	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Monthly migraine frequency	Brandes, 2006[30] Risk of bias Medium	4.1 [3.6]	50mg/day	4.5 [2.9]	-0.1 (-0.4 to 0.1)	-0.4 (-1.2 to 0.4)
Pooled with random effects	Risk of bias: Medium	Medium	50mg/day	Heterogeneity test: P value=0.9 I squared= 0%	-0.1 (-0.3 to 0.0)	-0.4 (-1.5 to 1.1)

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D21. Reduction in migraine severity and symptoms in randomized controlled clinical trials that examined efficacy of topiramate in adults

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Storey, 2001[18] Risk of bias Low	Mean migraine severity during treatment	200mg/day	19 [21]	2.0 [0.4]	2.0 [0.4]	-0.1 (-0.7 to 0.5)	0.0 (-0.3 to 0.2)
Silberstein, 2009[41] Risk of bias Low	Mean change in the rating of average daily headache severity	100 mg/day	165 [163]	-0.3 [0.6]	-0.2 [0.4]	-0.2 (-0.4 to 0.0)	-0.1 (-0.2 to 0.0)
	Change in worst daily headache severity	**100 mg/day**	**165 [163]**	**-0.4 [0.7]**	**-0.2 [0.5]**	**-0.3 (-0.5 to -0.1)**	**-0.2 (-0.3 to -0.1)**
	Mean decrease from baseline in the severity of nausea, photophobia, and phonophobia	100 mg/day	165 [163]	-0.2 [0.5]	-0.1 [0.4]	-0.2 (-0.4 to 0.0)	-0.1 (-0.2 to 0.0)
	Mean change from baseline in the monthly frequency of nausea	100 mg/day	165 [163]	-3.4 [5.8]	-2.3 [5.7]	-0.2 (-0.4 to 0.0)	-1.1 (-2.3 to 0.1)
	Mean change from baseline in the monthly rate of vomiting	100 mg/day	165 [163]	-1.0 [2.1]	-0.7 [2.6]	-0.1 (-0.3 to 0.1)	-0.3 (-0.8 to 0.2)
	Mean change from baseline in the monthly frequency of photophobia	100 mg/day	165 [163]	-5.0 [6.4]	-3.8 [5.6]	-0.2 (-0.4 to 0.0)	-1.2 (-2.5 to 0.1)
	Mean change from baseline in the monthly frequency of phonophobia	100 mg/day	165 [163]	-5.2 [6.0]	-3.6 [6.2]	-0.3 (-0.5 to 0.0)	-1.6 (-2.9 to -0.3)

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D22. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Silberstein, 2009[41] Risk of bias Low	**Mean change from baseline in the headache index (The headache index was calculated as the sum of the product of daily average headache severity multiplied by headache duration for the day, divided by the number of days in the specified period)**	**100 mg/day**	**165 [163]**	**-0.3 [0.3]**	**-0.2 [0.4]**	**-0.3 (-0.5 to -0.1)**	**-0.1 (-0.2 to 0.0)**
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire)scores: Emotional function domain	100 mg/day	165 [163]	-26.3 [27.8]	-21.0 [30.2]	-0.2 (-0.4 to 0.0)	-5.3 (-11.6 to 1.0)
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire) scores: Role Function Preventive domain	100 mg/day	165 [163]	-16.1 [21.5]	-12.6 [21.0]	-0.2 (-0.4 to 0.1)	-3.5 (-8.1 to 1.1)
	Mean change from baseline in the in the MSQ (Migraine Specific Questionnaire) scores: Role Function Restrictive domain	100 mg/day	165 [163]	-23.7 [23.1]	-18.8 [22.6]	-0.2 (-0.4 to 0.0)	-4.9 (-9.8 to 0.0)
	Mean change from baseline in the MIDAS (Migraine Disability Assessment) score	100 mg/day	165 [163]	-31.4 [53.8]	-21.0 [52.2]	-0.2 (-0.4 to 0.0)	-10.4 (-21.9 to 1.1)
Diener, 2007[38] Risk of bias Medium	**Mean change in HIT-6 (Headache Impact Test) questionnaire in the last 4 weeks of double-blind phase compared to open-label baseline**	**100mg/day**	**255 [259]**				**-1.9 (-3.4 to -0.4)**
	Mean change in SF-12 mental component score in the last 4 weeks of double-blind phase compared to open-label baseline	100mg/day	255 [259]				-1.2 (-3.4 to 1.0)
	Mean change in SF-12 physical health	100mg/day	255 [259]	-1.7	-3.1	NS	
	MIDAS score change at end-point	**50 to 200mg/day**	**32 [27]**	**-26.0 [61.0]**	**3.0 [21.0]**	**-0.6 (-1.1 to -0.1)**	**-29.0 (-51.6 to -6.4)**

Appendix Table D22. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Brandes, 2006[30] Risk of bias Medium	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	50mg/day	117 [114]	77.6 [22.71]	74.1 [21.35]	0.2 (-0.1 to 0.4)	3.5 (-2.2 to 9.2)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	**100 mg/day**	**120 [114]**	**82.9 [23.00]**	**74.1 [21.35]**	**0.4 (0.1 to 0.7)**	**8.8 (3.1 to 14.5)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-emotional function: at end of study	**200mg/day**	**117 [114]**	**82.7 [22.71]**	**74.1 [21.35]**	**0.4 (0.1 to 0.7)**	**8.6 (2.9 to 14.3)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	50mg/day	117 [114]	82.6 [18.39]	80.8 [17.08]	0.1 (-0.2 to 0.4)	1.8 (-2.8 to 6.4)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	**100 mg/day**	**120 [114]**	**85.5 [18.62]**	**80.8 [17.08]**	**0.3 (0.0 to 0.5)**	**4.7 (0.1 to 9.3)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: prevention: at end of study	**200mg/day**	**117 [114]**	**87.2 [18.39]**	**80.8 [17.08]**	**0.4 (0.1 to 0.6)**	**6.4 (1.8 to 11.0)**
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: restrictive: at end of study	50mg/day	117 [114]	71.9 [20.55]	67.2 [19.22]	0.2 (0.0 to 0.5)	4.7 (-0.4 to 9.8)
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating	**100 mg/day**	**120 [114]**	**75.8 [20.81]**	**67.2 [19.22]**	**0.4 (0.2 to 0.7)**	**8.6 (3.5 to 13.7)**

Appendix Table D22. Quality of life in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
	better functioning)-role function: restrictive: at end of study						
	MSQ (Migraine Specific Questionnaire: scored from 0 to 100 with higher scores indicating better functioning)-role function: restrictive: at end of study	**200mg/day**	**117 [114]**	**77.9 [18.39]**	**67.2 [17.08]**	**0.6 (0.3 to 0.9)**	**10.7 (6.1 to 15.3)**
Silberstein, 2006[27] Risk of bias Medium	**MSQ role function: prevention domain score at end point**	**100 mg/day**	**125 [115]**	**88.3 [15.7]**	**80.6 [16.1]**	**0.5 (0.2 to 0.7)**	**7.7 (3.7 to 11.7)**
	MSQ role function: prevention domain score at end point	200mg/day	112 [115]	84.4 [18.0]	80.6 [16.1]	0.2 (0.0 to 0.5)	3.8 (-0.6 to 8.2)
	MSQ role function: prevention domain score at end point	50mg/day	117 [115]	84.3 [16.2]	80.6 [16.1]	0.2 (0.0 to 0.5)	3.7 (-0.5 to 7.9)
	MSQ role function: restrictive domain score at end point	100 mg/day	125 [115]	77.2 [19.0]	65.8 [19.3]	0.6 (0.3 to 0.9)	11.4 (6.5 to 16.3)
	MSQ role function: restrictive domain score at end point	**200mg/day**	**112 [115]**	**75.8 [21.2]**	**65.8 [19.3]**	**0.5 (0.2 to 0.8)**	**10.0 (4.7 to 15.3)**
	MSQ role function: restrictive domain score at end point	**50mg/day**	**117 [115]**	**72.2 [19.5]**	**65.8 [19.3]**	**0.3 (0.1 to 0.6)**	**6.4 (1.4 to 11.4)**
	MSQ role function: emotional function score at end point	**100 mg/day**	**125 [115]**	**84.4 [21.2]**	**72.9 [21.4]**	**0.5 (0.3 to 0.8)**	**11.5 (6.1 to 16.9)**
	MSQ role function: emotional function score at end point	**200mg/day**	**112 [115]**	**81.2 [23.3]**	**72.9 [21.4]**	**0.4 (0.1 to 0.6)**	**8.3 (2.5 to 14.1)**
	MSQ role function: emotional function score at end point	**50mg/day**	**117 [115]**	**78.5 [21.6]**	**72.9 [21.4]**	**0.3 (0.0 to 0.5)**	**5.6 (0.1 to 11.1)**
Diamond, 2005[26] Risk of bias Low	**MSQ: Emotional domain: endpoint score**	**100 mg/day**	**384 [372]**	**82.5 [21.6]**	**73.5 [21.2]**	**0.4 (0.3 to 0.6)**	**9.0 (6.0 to 12.0)**
	MSQ: Prevention domain: endpoint score	**100 mg/day**	**384 [372]**	**85.5 [17.6]**	**79.9 [17.4]**	**0.3 (0.2 to 0.5)**	**5.6 (3.1 to 8.1)**
	MSQ: Restriction domain: endpoint score	**100 mg/day**	**384 [372]**	**75.4 [21.6]**	**66.5 [19.3]**	**0.4 (0.3 to 0.6)**	**8.9 (6.0 to 11.8)**

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0; SF-12 = Short Form 12-Item Health Survey; CI = confidence interval

Appendix Table D23. General health status in pooled analysis of individual patient data from randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (Medical Outcome Study Short Form 36 (SF-36) scores for each domain range from 0 to 100 with a higher score representing better function, a change of five points on the SF-36 is generally considered clinically meaningful)[37]

Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
SF-36: Bodily pain: change from baseline	**100 mg/day**	**384 [372]**	**11.5 [1.2]**	**4.6 [1.2]**	**5.8 (5.4 to 6.1)**	**6.9 (6.7 to 7.1)**
SF-36: General health: Change from baseline	**100 mg/day**	**384 [372]**	**2.2 [0.8]**	**0.8 [0.8]**	**1.8 (1.6 to 1.9)**	**1.4 (1.3 to 1.5)**
SF-36: Mental component summary: change from baseline	**100 mg/day**	**384 [372]**	**-0.2 [0.5]**	**0.1 [0.5]**	**-0.6 (-0.7 to -0.5)**	**-0.3 (-0.4 to -0.2)**
SF-36: Mental health: change from baseline	**100 mg/day**	**384 [372]**	**-0.5 [0.9]**	**-0.2 [0.9]**	**-0.3 (-0.5 to -0.2)**	**-0.3 (-0.4 to -0.2)**
SF-36: Physical component summary: change from baseline	**100 mg/day**	**384 [372]**	**4.7 [0.4]**	**2.5 [0.4]**	**5.5 (5.2 to 5.8)**	**2.2 (2.1 to 2.3)**
SF-36: Physical functioning: change from baseline	**100 mg/day**	**384 [372]**	**5.3 [0.8]**	**3.6 [0.9]**	**2.0 (1.8 to 2.2)**	**1.7 (1.6 to 1.8)**
SF-36: Role-emotional: change from baseline	**100 mg/day**	**384 [372]**	**2.3 [2.0]**	**3.0 [2.0]**	**-0.4 (-0.5 to -0.2)**	**-0.7 (-1.0 to -0.4)**
SF-36: Role-physical: change from baseline	**100 mg/day**	**384 [372]**	**17.9 [2.1]**	**12.0 [2.1]**	**2.8 (2.6 to 3.0)**	**5.9 (5.6 to 6.2)**
SF-36: Social functional: change from baseline	100 mg/day	384 [372]	4.8 [1.2]	4.8 [1.2]	0.0 (-0.1 to 0.1)	0.0 (-0.2 to 0.2)
SF-36: Vitality: change from baseline	**100 mg/day**	**384 [372]**	**5.2 [1.0]**	**1.8 [1.0]**	**3.4 (3.2 to 3.6)**	**3.4 (3.3 to 3.5)**

Bold = significant differences at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D24. Drug utilization for acute migraine attacks in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Mei, 2006[28] Risk of bias Low	**Amount of acute medication taken monthly**	**100 mg/day**	**30 [20]**	**3.2 [1.0]**	**15.4 [4.4]**	**-4.2 (-5.2 to -3.2)**	**-12.2 (-14.2 to -10.3)**
Diener, 2007[34] Risk of bias Medium	Change in number of days per month of acute medications intake	50 to 200mg/day	32 [27]	-3.0 [5.9]	-0.7 [6.2]	-0.4 (-0.9 to 0.1)	-2.3 (-5.4 to 0.8)
Silberstein, 2009[41] Risk of bias Low	Mean change from baseline in the number of days per month that subjects used acute headache medications	100 mg/day	165 [163]	-4.4 [5.8]	-3.4 [5.3]	-0.2 (-0.4 to 0.0)	-1.0 (-2.2 to 0.2)
Diener, 2007[38] Risk of bias Medium	Mean change in intake of acute medication in the last 4 weeks of double-blind phase compared to open-label baseline	100mg/day	255 [259]				-1.0 (-1.5 to -0.4)
Silberstein, 2004[23] Risk of bias Low	**Mean monthly Acute rescue medications days during the double-blind phase**	**100 mg/day**	**128 [117]**	**4.0 [3.4]**	**5.2 [3.3]**	**-0.4 (-0.6 to -0.1)**	**-1.2 (-2.0 to -0.4)**
	Mean monthly Acute rescue medications days during the double-blind phase	50mg/day	125 [117]	4.5 [3.1]	5.2 [3.3]	-0.2 (-0.5 to 0.0)	-0.7 (-1.5 to 0.1)
Brandes, 2004[22] Risk of bias Low	**Mean reduction in the monthly number of days when acute rescue medications were used**	**100 mg/day**	**122 [120]**	**-2.1 [3.20]**	**-1.0 [3.18]**	**-0.3 (-0.6 to -0.1)**	**-1.1 (-1.9 to -0.3)**
	Mean reduction in the monthly number of days when acute rescue medications were used	**200mg/day**	**121 [120]**	**-2.2 [3.19]**	**-1.0 [3.18]**	**-0.4 (-0.6 to -0.1)**	**-1.2 (-2.0 to -0.4)**

Appendix Table D24. Drug utilization for acute migraine attacks in randomized controlled clinical trials that examined efficacy of topiramate for migraine prevention in adults (continued)

Reference Risk of Bias	Definition of the Outcome	Daily Dose	Subjects in Active [Control] Groups	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Cohen Mean Difference (95% CI)	Mean Difference (95% CI)
Lipton, 2011[42] Risk of bias Low	**Number of days of acute medications use**	**100 mg/day**	**188 [197]**	**-4.8 [3.5]**	**-3.8 [3.7]**	**-0.3 (-0.5 to -0.1)**	**-1.0 (-1.7 to -0.3)**
Bussone, 2005[25] Risk of bias Low	**Percentage of migraine days with intake of medication to treat acute migraine attacks: from baseline to endpoint**	**100 mg/day**	**386 [372]**	**12.7 [0.6]**	**16.4 [0.6]**	**-6.7 (-7.1 to -6.4)**	**-3.7 (-3.8 to -3.6)**

Bold = significant differences at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D25. Randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Active Drug	Reference Sample Number Analyzed % Women	Definition of Migraine % without Aura	Baseline Severity	Age of Subjects (Eligible and Mean)	Years of Migraine % with prior Preventative Treatment
Divalproex	Mathew, 1995[45] Sample 107 Analyzed 105 % of women 77.6	Migraine (International Headache Society) % without aura: 95	Days per 4 week with migraine headaches during baseline phase: 7	16-75 Mean: 45.6	Years of migraine: 25 % with prior treatment: NR
Divalproex	Freitag, 2002[46] Sample 239 Analyzed 237 % of women 79	Migraine (International Headache Society) % without aura: 97	Days per 4 week with migraine headaches during baseline phase: 6.1	≥12 Mean: 40.5	Years of migraine: 20.2 % with prior treatment: NR
Divalproex	Klapper, 1997[47] Sample 176 Analyzed 171 % of women 89	Migraine (International Headache Society) % without aura: NR	Migraine attacks impairing usual activities during baseline (4 weeks): 5.8	≥16 Mean: 40.8	Years of migraine: 21.6 % with prior treatment: 53
Valproate	Hering, 1992[48] Sample 32 Analyzed 29 % of women 79.3	Migraine with aura (classical); patients suffering from migraine without aura (common); Ad Hoc Committee on Classification of Headache. % without aura: 13.7 (assumed)	From inclusion criteria: at least four attacks per months	NR (range: 18-54) Mean: 34	Years of migraine: 14 % with prior treatment: NR
Valproate	Jensen, 1994[49] Sample 43 Analyzed 34 % of women 86	Diagnosis of migraine without aura (International Headache Society) % without aura: 100	Mean frequency of migraines (4 weeks): 6.6	18-70 Mean: 46	Years of migraine: NR % with prior treatment: NR

NR = Not reported

Appendix Table D26. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Active drug	Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Divalproex	Mathew, 1995[45]	Industry	Yes	Yes	Yes	One author is employed by Abbott Laboratory, study funder.
Divalproex	Freitag, 2002[46]	Industry	Yes	Yes	Yes	Three authors are employed by Abbott Laboratory, study funder.
Divalproex	Klapper, 1997[47]	Industry	Not reported	Not reported	Yes	Five study participants are employed by Abbott Laboratory, study funder.
Valproate	Hering, 1992[48]	Not reported	Yes	Yes	Not reported	Not reported
Valproate	Jensen, 1994[49]	Industry	Yes	Yes	Not reported	Not reported

Appendix Table D27. Risk of bias in randomized controlled clinical trials that examined efficacy of divalproex or valproate for migraine prevention in adults

Reference	Masking of Treatment Status	Planned Intention to Treat	Allocation Concealment	Adequacy of Randomization	Baseline Migraine Similarity	Selective Outcome Reporting	Risk of Bias
Mathew, 1995[45]	DB	No	Unclear	Yes	D	No	Medium
Freitag, 2002[46]	DB	Yes	Unclear	Yes	F, S & D	No	Low
Klapper, 1997[47]	DB	Yes	Unclear	Yes	D	No	Low
Hering, 1992[48]	DB	No	Unclear	Not reported	Not reported	No	Medium
Jensen, 1994[49]	TB	No	Unclear	Yes	F, S & D	No	Medium

DB = double blind
TB = triple blind
D = duration
F = frequency
S = severity

Appendix Table D28. Strength of evidence of migraine prevention in adults with divalproex vs. placebo, results from randomized controlled clinical trials

Outcome	Daily Dose	Reference	Sample	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
≥ 50% reduction in migraine headache rate		Mathew, 1995[45] Freitag, 2002[46] Klapper, 1997[47]						
≥ 50% reduction in migraine headache rate		Pooled	405	Medium	Yes	No	No	Low
50% improvement in migraine attacks impairing usual activities	500 mg	Klapper, 1997[47]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks impairing usual activities	1000 mg	Klapper, 1997[47]	58	Low	Yes	NA	No	Low
50% improvement in migraine attacks impairing usual activities	1500 mg	Klapper, 1997[47]	59	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	500 mg	Klapper, 1997[47]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg	Klapper, 1997[47]	57	Low	Yes	NA	No	Low
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg	Klapper, 1997[47]	59	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	500 mg	Klapper, 1997[47]	60	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1000 mg	Klapper, 1997[47]	58	Low	Yes	NA	No	Low
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1500 mg	Klapper, 1997[47]	59	Low	Yes	NA	No	Low

NA = not applicable

Appendix Table D29. Migraine prevention in adults with divalproex vs. placebo, results from randomized controlled clinical trials

Outcome	Daily Dose	Reference Risk of Bias	Events/Randomized with Divalproex	Events/Randomized with Placebo	Rate,% with Divalproex [Placebo]	Relative Risk (95%CI)	Absolute Risk Difference (95%CI)
≥50% reduction in migraine headache rate		Mathew, 1995[45] Medium	33/70	5/37	47.1 [13.5]	3.5 (1.5 to 8.2)	0.34 (0.18 to 0.50)
≥50% reduction in migraine headache rate		Freitag, 2002[46] Low	50/123	32/116	40.7 [27.6]	1.5 (1.0 to 2.1)	0.13 (0.01 to 0.25)
≥50% reduction in migraine headache rate		Klapper, 1997[47] Low	19/44	2/15	43.2 [13.6]	3.2 (0.9 to 12.3)	0.30 (0.07 to 0.52)
≥50% reduction in migraine headache rate	1,000-1,500mg	**Medium**	102/237	39/168	43.0 [23.3]	2.2 (1.1 to 4.2)	0.24 (0.10 to 0.38)
≥50% reduction in migraine headache rate	Heterogeneity P value					0.098	0.108
≥50% reduction in migraine headache rate	Heterogeneity P value I squared					56.90%	55.10%
50% improvement in migraine attacks impairing usual activities	500 mg	Klapper, 1997[47] Risk of bias Low	26/45	4/15	57.8 [25.0]	2.2 (0.9 to 5.2)	0.31 (0.04 to 0.58)
50% improvement in migraine attacks impairing usual activities	1000 mg	Klapper, 1997[47] Risk of bias Low	16/43	4/14	37.2 [25.0]	1.4 (0.6 to 3.5)	0.11 (-0.16 to 0.37)
50% improvement in migraine attacks impairing usual activities	1500 mg	Klapper, 1997[47] Risk of bias Low	24/44	4/15	54.5 [25.0]	2.0 (0.8 to 4.9)	**0.28 (0.01 to 0.55)**
50% improvement in migraine attacks necessitating symptomatic medication	500 mg	Klapper, 1997[47] Risk of bias Low	19/45	2/15	42.2 [13.6]	3.2 (0.8 to 12.0)	**0.29 (0.06 to 0.51)**

Appendix Table D29. Migraine prevention in adults with divalproex vs. placebo, the results from randomized controlled clinical trials (continued)

Outcome	Daily Dose	Reference Risk of Bias	Events/Randomized with Divalproex	Events/Randomized with Placebo	Rate,% with Divalproex [Placebo]	Relative Risk (95%CI)	Absolute Risk Difference (95%CI)
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg	Klapper, 1997[47] Risk of bias Low	16/43	2/14	37.2 [13.6]	2.6 (0.7 to 10.0)	0.23 (0.00 to 0.46)
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg	Klapper, 1997[47] Risk of bias Low	19/44	2/15	43.2 [13.6]	3.2 (0.9 to 12.3)	**0.30 (0.07 to 0.52)**
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	500 mg	Klapper, 1997[47] Risk of bias Low	21/45	3/15	46.7 [18.2]	2.3 (0.8 to 6.7)	**0.27 (0.02 to 0.52)**
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1000 mg	Klapper, 1997[47] Risk of bias Low	18/43	3/14	41.9 [18.2]	2.1 (0.7 to 6.1)	0.22 (-0.03 to 0.47)
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	**1500 mg**	Klapper, 1997[47] **Risk of bias Low**	**22/44**	**3/15**	**50.0 [18.2]**	**2.5 (0.9 to 7.2)**	**0.30 (0.05 to 0.55)**

Bold = significant at 95% confidence limit 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level

Appendix Table D30. Migraine frequency, severity, and drug utilization with valproate vs. placebo for migraine prevention in adults, results from medium risk of bias randomized controlled clinical trials

Outcome	Daily Dose	Reference	Mean [Standard deviation] with Valproate	Mean [Standard deviation] with Placebo	Randomized to Valproate vs. Placebo	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Mean number of days with migraine	1000mg to 1500 mg per day	Jensen, 1994[49]	3.5 [4.8]	6.1 [7.7]	43 [43]	-2.6 (-5.3 to 0.1)	-0.4 (-0.8 to 0.0)
Total drug consumption	**1000mg to 1500 mg per day**	Jensen, 1994[49]	**NR [NR]**	**NR [NR]**	**43 [43]**	**p value <0.001**	
Consumption of symptomatic medication per attack	1000mg to 1500 mg per day	Jensen, 1994[49]	NR [NR]	NR [NR]	43 [43]	p value 0.61	
Mean number of attacks (4 weeks)	**400 mg twice a day**	Hering, 1992[48]	**8.8 [6.1]**	**15.6 [8.3]**	**32 [32]**	**-6.8 (-10.3 to -3.2)**	**-0.9 (-1.4 to -0.4)**
Duration of the remaining attack (hours)	1000mg to 1500 mg per day	Jensen, 1994[49]	11.1 [NR]	11.5 [NR]	43 [43]	p value 0.9	
Duration of the attack (total hours)	**400 mg twice a day**	Hering, 1992[48]	**1731.0 [NR]**	**2789.0 [NR]**	**32 [32]**	**p value = 0.002**	
Intensity of the remaining attacks (no details provided)	1000mg to 1500 mg per day	Jensen, 1994[49]	2.3 [NR]	2.3 [NR]	43 [43]	p value0.45	
Mean number of severe migraine attacks (4 weeks)	**400 mg twice a day**	Hering, 1992[48]	**14.6 [9.8]**	**24.0 [15.4]**	**32 [32]**	**-9.4 (-15.7 to -3.1)**	**-0.7 (-1.2 to -0.2)**

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence level
NR = not reported

Appendix Table D31. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
Diamond, 1976[50] Sample 83 80.7% women	To evaluate propranolol in the prophylaxis of migraine	Classic or common migraine (Ad Hoc Committee)	Not reported	Mean: 38.1	Not reported
Stensrud, 1976[51] Stensrud, 1976[51] Sample 20 70% women	To investigate the effects of propranolol in the racemic form (Inderal) and d-propranolol.	Common and classic migraine (as defined by the Ad Hoc Committee)	Not reported	43.5	Not reported
Forssman, 1976[52] Sample 40 87.5% women	To compare the preventive effect of propranolol on migraine attacks with placebo in a double-blind crossover trial	Not reported	18.9	Mean: 37.4	Not reported
Pradalier, 1989[53] Sample 55 76% women	To evaluate the efficacy and tolerability of long-acting propranolol in migraine	International Headache Society	Not reported	Mean: 37.4	Mean frequency of migraine (month): 4
Nadelman, 1986[54] Sample 57 85.5% women	To compare the relative efficacy and safety of propranolol with that of placebo in the prophylaxis of migraine headache	Classic and/or common migraine headaches as set forth by the Ad Hoc Committee on the Classification of Headache	1-5: 22.6%; 6-10: 27.4%; 11-15: 14.5%; 16-20: 9.7%; 21-25: 8.1%; 26+: 17.7%	Not reported	Headache Unit Index: 1.09
Sargent, 1985[55] Sample 149 79% women	To evaluate the prophylactic effect and tolerance of naproxen sodium compared to propranolol hydrochloride and placebo in migraine	Common or classical migraine, or a combination migraine and muscle contraction headache (no definition provided)	20	Mean: 30	Not reported
Ahuja, 1985[56] Sample 26 46.2% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
Malvea, 1973[57] Sample 31 87% women	To determine the relative effectiveness of propranolol in the prevention of migraine as compared to a placebo in a double-blind trial	Not reported	Not reported	Not reported (ranges: 25-57)	Average headache units: 25.4 (no definition provided)

Appendix Table D31. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
Wideroe, 1974[58] Sample 30 86.7% women	To investigate the value of propranolol in preventing attacks of migraine	Classic or common migraine (Ad Hoc Committee, 1962)	Not reported	Mean: 40	All except four patients had two or more attacks a month
Palferman, 1983[59] Sample 36 80% women	To assess the efficacy of prophylactic propranolol on the severity and frequency of their symptoms	Episodic headache with other accepted disorders of cerebral function including visual disturbances and vomiting	17.5 (all patients: 11.3)	Mean: 41.4 (all patients: 37.8)	Not reported
Tfelt-Hansen, 1984[60] Sample 96 74% women	To compare the beta-adrenergic blocker timolol to an established drug, propranolol, and to placebo for prophylactic effect in common migraine	Between 2 and 6 common migraine attacks per month as defined by the ad hoc committee and by Olsen	20.9	Mean: 39.5	Number of migraine attacks per 4 weeks: 5.7
Standnes, 1982[61] Sample 25 80% women	To evaluate the prophylactic effect of timolol in migraine	Common migraine attacks (as defined by the Ad Hoc Committee)	Not reported	Mean: 41.4	Mean number of attacks (4 weeks): 6.65
Stensrud, 1980[62] Sample 35 68.6% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
al-Qassab, 1993[63] Sample 45 80% women	To assess the effectiveness of two different doses of a long-acting formulation of propranolol (propranolol LA) in patients with severe migraine	Diagnosis of migraine was made on clinical assessment.	Median: 9	Median: 36	Median attacks (month): 4
Diener, 2004[43] Sample 575 79.8% women	To evaluate the efficacy and safety of two doses of topiramate and safety of two doses of topiramate vs. placebo for migraine prophylaxis, with propranolol (PROP) as an active control	International Headache Society	Not reported	Median: 41	Mean monthly migraine frequency: 5.1

Appendix Table D31. Randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
Rafieian-Kopaei, 2005[64] Sample 105 % women Not reported	To compare the prophylactic activity of propranolol and amitriptyline on frequency, duration and severity of migraine attacks	Migraine (International Headache Society)	>1 (from inclusion criteria)	Not reported	Mean attack frequency: 4.02 (per month)
Weber, 1972[65] Sample 25 52% women	To compare the prophylactic effect of the propranolol to placebo	Migraine (Classification of headache, JAMA (1962) 179, 717)	Not reported	Mean: 40.6	Not reported
Pradalier, 1989[66] Sample 55 75.7% women	To assess the efficacy and safety of long-acting propranolol (LA. P) 160 mg once-daily in the prophylactic treatment of migraine	Migraine (International Headache Society)	Not reported	Not reported	Not reported
Kuritzky, 1987[67] Sample 38 % women Not reported	1) To evaluate the efficacy of long acting propranolol (Deralin SR) in reducing the frequency, duration and severity of migraine when compared with placebo, 2) To register possible side effects, and 3) to study correlation between plasma propranolol levels and clinical effectiveness in migraine.	Not reported (While eligibility criteria are not reported, author described "classic or common migraine" patients were included.)	14.2	Not reported	Mean number of migraine attacks: 3 (""All patients averaged at least 3 attacks per month when untreated.")

Appendix Table D32. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed - Relationships
Diamond, 1976[50]	Not reported	Not reported	Yes	Not reported	Not reported
Stensrud, 1976[51]	Not reported	Not reported	Not reported	Not reported	Not reported
Forssman, 1976[52]	Not reported	Not reported	Not reported	Not reported	Not reported
Pradalier, 1989[53]	Not reported	Not reported	Yes	Not reported	Not reported
Nadelmann, 1986[54]	Not reported	Not reported	Yes	Unclear	Two authors are employed by pharmaceutical industry (Ayerst Laboratories), but unclear their relationship (no funding source reported.)
Sargent, 1985[55]	Not reported	Not reported	Not reported	Not reported	Not reported
Ahuja, 1985[56]	Industry (Inderal brand of propranolol and identical looking placebo tablets were supplied by Alkali and Chemical Corp. India Ltd.	Not reported	Not reported	Not reported	Not reported
Malvea, 1973[57]	Industry	Not reported	Not reported	Not reported	Not reported
Wideroe, 1974[58]	Not reported	Not reported	Not reported	Not reported	Not reported
Palferman, 1983[59]	Industry (all tablets were supplied by ICI Pharmaceuticals)	Not reported	Not reported	Not reported	Not reported
Tfelt-Hansen, 1984[60]	Not reported	Not reported	Yes	Not reported	Not reported
Standnes, 1982[61]	Industry	Not reported	Yes	Not reported	Not reported
Stensrud, 1980[62]	Not reported	Not reported	Not reported	Not reported	Not reported
al-Qassab, 1993[63]	Industry	Yes	Yes	Not reported	Not reported
Diener, 2004[43]	Industry	Yes	Yes	Yes	Hans-Christoph Diener has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from 3M Medica, Allergan, Almirall Prodesfarma, AstraZeneca, Bayer Vital, Böhringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, La Roche, Lilly, Novartis, MSD, Parke-Davis, Pfizer, Pharmacia, Pierre Fabre, Schaper and Brümmer, and Weber & Weber. Peer Tfelt-Hansen has been a consultant/scientific advisor for, and/or has received honoraria for oral presentation from Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, MSD, Pfizer, and Quintiles. Carl Dahlöf has been a

Appendix Table D32. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults (continued)

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed - Relationships
					consultant/scientific advisor for, and has received honoraria for oral presentations from Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Jansen-Cilag, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Pharmacia, and Pierre Fabre. Miguel JA Láinez has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Almirall Prodesfarma, AstraZeneca, Böhringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, MSD, Novartis, Pfizer, Pierre Fabre, and Sanofi-Synthelabo. Giorgio Sandrini has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Allergan, AstraZeneca, Bayer, Bristol- Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, Lilly, MSD, Pfizer, Pharmacia, and Solvay Pharma. Shuu-Jiun Wang has received grant/research support from and/or received honoraria for oral presentations from AstraZeneca, Glaxo- SmithKline, Johnson & Johnson, Lilly, MSD, and Pfizer. Walter Neto, Ujjwalla Vijapurkar, Aiden Doyle, and David Jacobs are employed by Johnson & Johnson Pharmaceutical Research and Development, LLC.
Rafieian-Kopaei, 2005[64]	Other	Not reported	Yes	Not reported	All authors are from the University that sponsored the study
Weber, 1972[65]	Industry (drugs were provided by Ayerst laboratories)	Not reported	Not reported	Unclear	Dr. Trent and Kyle of Ayerst laboratories assisted in the study. Their contribution not known.
Pradalier, 1989[66]	Not reported	Not reported	Not reported	Not reported	Not reported
Kuritzky, 1987[67]	Not reported	Yes	Yes	Not reported	Not reported

Appendix Table D33. Risk of bias in randomized controlled clinical trials that examined efficacy of propranolol for migraine prevention in adults

Reference	Masking Treatment Status	Planned Intention to Treat	Allocation Concealment	Adequacy of Randomization	Baseline Similarity by Migraine Status	Selective Outcome Reporting	Risk of Bias
Diamond, 1976[50]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Stensrud, 1976[51]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Forssman, 1976[52]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Pradalier, 1989[53]	Double blind	Yes	Unclear	Yes	F & S	Unclear	Low
Nadelmann, 1986[54]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Sargent, 1985[55]	Double blind	No	Unclear	Yes	Not reported	Unclear	Medium
Ahuja, 1985[56]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Low
Malvea, 1973[57]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Wideroe, 1974[58]	Double blind	No	Unclear	Not reported	S	Unclear	Medium
Palferman, 1983[59]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Tfelt-Hansen, 1984[60]	Double blind	No	Unclear	Yes	F, S & D	Unclear	Medium
Standnes, 1982[61]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Stensrud, 1980[62]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
al-Qassab, 1993[63]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Diener, 2004[43]	Double blind	Yes	Unclear	Yes	F	Unclear	Low
Rafieian-Kopaei, 2005[64]	Double blind	No	Unclear	Not reported	F	Unclear	Medium
Weber, 1972[65]	Double blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Pradalier, 1989[66]	Double blind	Yes	Unclear	Not reported	Not reported	Unclear	Low
Kuritzky, 1987[67]	Open-label	No	Unclear	Not reported	Not reported	Unclear	High

F = monthly migraine frequency; S = migraine severity; D = migraine duration

Appendix Table D34. Strength of evidence of migraine prevention with propranolol (randomized controlled clinical trials)

Reference	Active Drug	Control Drug	Sample Size	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Tfelt-Hansen, 1984[60]				Medium				
Diener, 2004[43]				Low				
Diamond, 1976[50]				Medium				
Standnes, 1982[61]				Medium				
Pooled	Propranolol	Placebo	541	Medium	Yes	Consistent	No	Low
Diener, 2004[43]	Topiramate	Propranolol	288	Low	Yes	Not applicable	No	Low
Kaniecki, 1997[68]	Divalproex	Propranolol	74	High	Yes	Not applicable	No	Insufficient
Kass, 1980[69]	Propranolol	Clonidine	46	Medium	Yes	Not applicable	No	Low
Kangasniemi, 1984[70]				Medium				
Gerber, 1991[71]				Medium				
Pooled	Propranolol	Metoprolol.	113	Medium	Yes	Yes	No	Low
Sudilovsky, 1987[72]	Propranolol	Nadolol	93	Medium	Yes	Not applicable	No	Low
Olerud, 1986[73]	Nadolol	Propranolol	28	Medium	Yes	Not applicable	No	Low
Tfelt-Hansen, 1984[60]				Medium				
Standnes, 1982[61]				Medium				
Pooled	Timolol	Propranolol	242	Medium	Yes	Yes	No	Low
Gerber, 1991[71]	Propranolol	Nifedipine	36	Medium				Low
Albers, 1989[74]	Propranolol	Nifedipine	40	High				Low
Pooled	Propranolol	Nifedipine	76	High	Yes	Yes	No	Low
Domingues, 2009[75]	Propranolol	Nortriptyline	49	Medium	Yes	Not applicable	No	Low
Ziegler, 1987[76]	Propranolol	Amitriptyline	108	Medium	Yes	Not applicable	Yes	Low
Kangasniemi, 1983[77]	Propranolol	Femoxetine	29	Medium	Yes	Not applicable	No	Low
Domingues, 2009[75]	Nortriptyline	Propranolol + Nortriptyline	51	Medium	Yes	Not applicable	No	Low
Domingues, 2009[75]	Propranolol	Propranolol + Nortriptyline	52	Medium	Yes	Not applicable	No	Low
Silberstein, 2012[78]	Propranolol	Propranolol+ Topiramate	191	Medium	Yes	Not applicable	No	Low

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥50% reduction of average monthly migraine frequency	Tfelt-Hansen, 1984[60] Medium	80 mg b.i.d. (plus timolol placebo)	Placebo	48/96	12/48	50.0 [25.0]	2.0 (1.2 to 3.4)	0.25 (0.09 to 0.41)
≥50% reduction of average monthly migraine frequency	Diener, 2004[43] Low	160 mg/d	Placebo	62/144	11/49	43.1 [21.9]	1.9 (1.1 to 3.3)	0.21 (0.06 to 0.35)
≥50% reduction of average monthly migraine frequency	Diamond, 1976[50] Medium	80 or 160 mg	Placebo	34/83	17/83	41.0 [20.5]	2.0 (1.2 to 3.3)	0.21 (0.07 to 0.34)
≥50% reduction of average monthly migraine frequency	Standnes, 1982[61] Medium	80 mg + (timolol placebo)	Placebo	13/25	3/13	52.0 [24.0]	2.3 (0.8 to 6.5)	0.29 (-0.01 to 0.59)
≥50% reduction of average monthly migraine frequency	**Pooled Medium**	**80-160mg**	**Placebo**	**157/348**	**43/193**	**45.1 [22.3]**	**2.0 (1.5 to 2.7)**	**0.22 (0.14 to 0.30)**
Heterogeneity							P value = 0.9 I squared = 0%	P value = 0.9 I squared = 0%
≥50% reduction of average monthly migraine frequency	Diener, 2004[43] Risk of bias Low	Topiramate 100 mg/d	Propranolol 160 mg/d	52/141	62/144	36.9 [43.1]	0.9 (0.6 to 1.1)	-0.06 (-0.18 to 0.05)

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥ 50% reduction of average monthly migraine frequency	Diener, 2004[43] Risk of bias Low	Topiramate 200 mg/d	Propranolol 160 mg/d	50/144	62/144	34.7 [43.1]	0.8 (0.6 to 1.1)	-0.08 (-0.20 to 0.03)
Greater than 50% reduction in 28 day rate of moderate to severe headaches	Silberstein, 2012[78] Risk of bias medium	Propranolol, 240 mg/day + topiramate 88 mg/day	Topiramate 88 mg/day	26/96	23/95	27 [24]	1.1 (0.7 to 1.8)	0.03 (-0.10 to 0.15
Patients responding with a 50% or greater reduction in mean migraine frequency (month)	Kaniecki, 1997[68] Risk of bias High	Divalproex Mean dose: 1414mg/d	Propranolol Mean dose: 174mg/d	21/37	20/37	56.8 [54.1]	1.1 (0.7 to 1.6)	0.03 (-0.20 to 0.25)
Patients responding with a 50% or greater reduction in mean migraine days (month)	Kaniecki, 1997[68] Risk of bias High	Divalproex Mean dose: 1414mg/d	Propranolol Mean dose: 174mg/d	21/37	22/37	56.8 [59.5]	1.0 (0.6 to 1.4)	-0.03 (-0.25 to 0.20)
>50% reduction of headache days, 4 weeks (comparing pretreatment period with the last 4 wks of treatment)	Kass, 1980[69] Risk of bias Medium	Propranolol 160 mg (two 40 mg tablets twice daily)	Clonidine 100 µg (two 25 µg tablets twice daily)	13/23	8/23	56.5 [34.8]	1.6 (0.8 to 3.2)	0.22 (-0.06 to 0.50)

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥50% reduction of the sum of severity scores	Kangasniemi, 1984[70] Risk of bias Medium	Propranolol 80 mg b.i.d.	Metoprolol 200 mg o.m.	15/36	17/36	41. 7 [47.2]	0.9 (0.5 to 1.5)	-0.06 (-0.29 to 0.17)
Responder of Migraine days	Gerber, 1991[71] Risk of bias Medium	Propranolol Hydrochloride 160 m/day (HD)	Metoprolol 200 mg / day (HD)	6/19	12/22	31.6 [54.5]	0.6 (0.3 to 1.2)	-0.23 (-0.53 to 0.07)
	Pooled with random effects model	Propranolol	Metoprolol	21/55	29/58	38.2 [50.0]	0.8 (0.5 to 1.2)	-0.12 (-0.30 to 0.06)
	Heterogeneity						p=0.371 (I-squared (variation in RR Attributable Due heterogeneity)=0.0%	p=0.361 (I-squared (variation in RD Attributable Due heterogeneity)=0.0%
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	4/44	13/49	9.1 [26.5]	0.3 (0.1 to 1.0)	-0.17 (-0.32 to -0.02)
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[72] **Risk of bias Medium**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**4/44**	**17/47**	**9.1 [36.2]**	**0.3 (0.1 to 0.7)**	**-0.27 (-0.43 to -0.11)**
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	5/44	11/49	11.4 [22.4]	0.5 (0.2 to 1.3)	-0.11 (-0.26 to 0.04)
≥50% reduction of frequency of distinct headache	Sudilovsky, 1987[72] **Risk of bias Medium**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**5/44**	**18/47**	**11.4 [38.3]**	**0.3 (0.1 to 0.7)**	**-0.27 (-0.44 to -0.10)**
≥50% reduction of headache intensity	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	8/44	14/49	18.2 [28.6]	0.6 (0.3 to 1.4)	-0.10 (-0.27 to 0.07)

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥50% reduction of headache intensity	Sudilovsky, 1987[72] **Risk of bias Medium**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**8/44**	**19/47**	**18.2 [40.4]**	**0.4 (0.2 to 0.9)**	**-0.22 (-0.40 to -0.04)**
≥50% reduction of headache intensity	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	10/44	11/49	22.7 [22.4]	1.0 (0.5 to 2.2)	0.00 (-0.17 to 0.17)
≥50% reduction of headache intensity	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 160 mg o.d.	10/44	21/47	22.7 [44.7]	0.5 (0.3 to 1.0)	**-0.22 (-0.41 to -0.03)**
≥50% reduction of pain days	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	8/44	9/49	18.2 [18.4]	1.0 (0.4 to 2.3)	0.00 (-0.16 to 0.16)
≥50% reduction of pain days	Sudilovsky, 1987[72] **Risk of bias Medium**	**Propranolol Hydrochloride 80 mg b.i.d.**	**Nadolol 160 mg o.d.**	**8/44**	**19/47**	**18.2 [40.4]**	**0.4 (0.2 to 0.9)**	**-0.22 (-0.40 to -0.04)**
≥50% reduction of pain days	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 80 mg o.d.	9/44	11/49	20.5 [22.4]	0.9 (0.4 to 2.0)	-0.02 (-0.19 to 0.15)
≥50% reduction of pain days	Sudilovsky, 1987[72] Risk of bias Medium	Propranolol Hydrochloride 80 mg b.i.d.	Nadolol 160 mg o.d.	9/44	18/47	20.5[38.3]	0.5 (0.3 to 1.1)	-0.18 (-0.36 to 0.00)
>50% reduction of number of migraine attacks compared to placebo period	Sudilovsky, 1987[72] Risk of bias Medium	Nadolol 80 mg/daily (every morning + matching placebo tablet every night)	Propranolol 80 mg (40 mg twice daily)	5/13	9/15	38.5 [60.0]	0.6 (0.3 to 1.4)	-0.22 (-0.58 to 0.15)
Responder of Migraine days	Gerber, 1991[71] Risk of bias Medium	Propranolol Hydrochloride 80 mg/day	Nifedipine 20 mg/day	0/19	0/17	0.0 [0.0]	0.0 (0.0 to 0.0)	0.00 (-0.10 to 0.10)

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Responder of Migraine days	Gerber, 1991[71] Risk of bias Medium	Propranolol Hydrochloride 40 mg/day	Nifedipine 10 mg/day	3/19	0/17	15.8 [0.0]	6.3 (0.3 to 113.8)	0.16 (-0.03 to 0.34)
Responder of Migraine days	Gerber, 1991[71] Risk of bias Medium	Propranolol Hydrochloride 120 mg/day	Nifedipine 30 mg/day	4/19	2/17	21.1 [11.8]	1.8 (0.4 to 8.6)	0.09 (-0.15 to 0.33)
Responder of Migraine days	Gerber, 1991[71] Risk of bias Medium	Propranolol Hydrochloride 160 mg/day	Nifedipine 40 mg/day	6/19	1/17	31.6 [5.9]	5.4 (0.7 to 40.2)	0.26 (0.02 to 0.49)
Drug efficacy: >50% improvement	Albers, 1989[74] Risk of bias High	Propranolol 60 mg TID	Nifedipine 30 mg TID	12/20	6/20	60.0 [30.0]	2.0 (0.9 to 4.3)	0.30 (0.01 to 0.59)
Reduction by 50% or more in migraine days	**Pooled with random effects models**[71, 74]	**Propranolol 160-180mg**	**Nifedipine**	18/39	7/37	46.2 [18.9]	**2.3 (1.1 to 4.6)**	**0.27 (0.09 to 0.46)**
	Heterogeneity						p=0.368 (I-squared (variation in RR Attributable Due heterogeneity)=0.0%	p=0.823 (I-squared (variation in RD Attributable Due heterogeneity)=0.0%
≥50% reduction of the number of days with headache	Domingues, 2009[75] Risk of bias Medium	Propranolol 40 mg/d	Nortriptyline 20 mg/d	11/25	7/24	33.3 [39.3]	1.5 (0.7 to 3.2)	0.15 (-0.12 to 0.41)
Good response: fall in headache score (compared with placebo treatment) of 50% or more	Ziegler, 1987[76] Risk of bias Medium	Propranolol 80-240 mg/d	Amitriptyline 50-150 mg/d	12/54	10/54	19.2 [21.4]	1.2 (0.6 to 2.5)	0.04 (-0.11 to 0.19)
>50% reduction of frequency of attack	Kangasniemi, 1983[77] Risk of bias Medium	Propranolol 80 mg twice a day	Femoxetine 200 mg twice a day	3/15	1/14	20.0 [7.1]	2.8 (0.3 to 23.9)	0.13 (-0.11 to 0.37)

Appendix Table D35. Migraine prevention with propranolol, results from randomized controlled clinical trials (continued)

Definition Outcomes	Reference Risk of Bias	Active Drug, Daily Dose	Control, Daily Dose	Events/ Randomized with Active Drug	Events/ Randomized with Control	Rate,% with Active [Control] Treatments	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥50% reduction of the number of days with headache	Domingues, 2009[75] Risk of bias Medium	Nortriptyline 20 mg/d	Propranolol + Nortriptyline	7/24	10/27	29.2 [37.0]	0.8 (0.4 to 1.7)	-0.08 (-0.34 to 0.18)
≥ 50% reduction of the number of days with headache	Domingues, 2009[75] Risk of bias Medium	Propranolol 40 mg/d	Propranolol + Nortriptyline	11/25	10/27	44.0 [37.0]	1.2 (0.6 to 2.3)	0.07 (-0.20 to 0.34)

Bold = significant at 95% confidence limit. Bold differences are statistically significant when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D36. Reduction in frequency of migraine attack by ≥50% from baseline with timolol 10mg twice a day (pooled with random effects model results from randomized controlled clinical trials)

Reference Risk of Bias	Events/ Randomized with Active Drug	Events/ Randomized with Placebo	Rate,% with Active Drug [Placebo]	Relative Risk (95% CI)	Weight, Random Effects Inverse Variance	Absolute Risk Difference (95% CI)	Weight, Random Effects Inverse Variance
Tfelt-Hansen, 1984[60] Medium	44/96	12/48	45.8[25.0]	1.8 (1.1 to 3.1)	49.32	0.21 (0.05 to 0.37)	49.78
Standnes, 1982[61] Medium	14/25	3/13	56.0[24.0]	2.4 (0.8 to 6.9)	12.82	0.33 (0.03 to 0.63)	13.75
Stellar, 1984[79] Medium	25/47	10/47	53.2[21.3]	2.5 (1.4 to 4.6)	37.86	0.32 (0.14 to 0.50)	36.47
Pooled	**83/168**	**25/108**	**49.4[23.3]**	**2.1 (1.5 to 3.1)**	**100**	**0.27 (0.15 to 0.38)**	**100**
Heterogeneity test				p = 0.732	I-squared=0.0%	p = 0.606	I-squared = 0.0%

CI = confidence interval. Bold- differences are statistically significant when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D37. Strength of evidence of migraine prevention with timolol

Sample Size, References	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Tfelt-Hansen, 1984[60] Standnes, 1982[61] Stellar, 1984[79] 276[60, 61, 79]	Medium	Yes	Yes	No	Low

Appendix Table D38. Reduction in migraine attack frequency and severity with timolol 10mg twice a day (results from randomized controlled clinical trial[60])

Outcomes	Mean [Standard Deviation] with Drug	Mean [Standard Deviation] with Placebo	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)	Mean Ratio (95% CI)
Frequency of attacks	**3.4 [3.1]**	**4.8 [3.9]**	**-1.5 (-2.5 to -0.5)**	**-0.4 (-0.7 to -0.1)**	**0.7 (0.5 to 1.0)**
Number of attacks (4 weeks)	**2.8 [NR]**	**4.7 [NR]**	**P<0.01**		
Duration of attacks (hours)	7.4 [7.3]	8.0 [6.7]	-0.5 (-2.5 to 1.4)	-0.1 (-0.4 to 0.2)	0.9 (0.7 to 1.3)
Frequency of attacks with any therapy	**2.8 [3.0]**	**4.2 [3.7]**	**-1.4 (-2.4 to -0.4)**	**-0.4 (-0.7 to -0.1)**	**0.7 (0.5 to 0.9)**
Frequency of attacks with nausea	1.4 [1.9]	1.9 [2.1]	-0.5 (-1.0 to 0.1)	-0.2 (-0.5 to 0.0)	0.7 (0.6 to 0.9)
Headache index (2) (frequency x average severity)	**41.7 [50.2]**	**69.3 [69.4]**	**-27.6 (-44.7 to -10.5)**	**-0.5 (-0.7 to -0.2)**	**0.6 (0.5 to 0.8)**
Headache index (1) (frequency x average severity)	**5.7 [5.1]**	**9.0 [7.3]**	**-3.3 (-5.1 to -1.5)**	**-0.5 (-0.8 to -0.2)**	**0.6 (0.5 to 0.9)**
Severity of attacks	**1. 8 [0.6]**	**1.9 [0.5]**	**-0.2 (-0.3 to 0.0)**	**-0.4 (-0.6 to -0.1)**	0.9 (0.3 to 2.6)

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D39. Randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Active Drug	Reference Sample Number Analyzed % Women	Definition of Migraine % Without Aura	Baseline Severity	Eligible Age of Subjects	Years of Migraine % with prior Preventative Treatment
Acetazolamide	Vahedi, 2002[80] Sample 53 Analyzed 53 % of women 75.5	Migraine (International Headache Society) % without aura 90.6	Attack frequency (4wks): 5	18-65 Mean: 39.2	Years of migraine NR % with prior treatment NR
Gabapentin	Mathew, 2001[81] Sample 145 Analyzed 87 % of women 82.8	Migraine (International Headache Society) % without aura 56.3	Migraine headache frequency during last 6 months: 4.9	16-75 Mean: 39.6	Years of migraine 20.8 % with prior treatment NR
Vigabatrin	Ghose, 2002[82] Sample 23 Analyzed 15 % of women 73.9	Migraine (International Headache Society) % without aura 56.5	Headache frequency (1 week): 2.14	NR (range: 18-66) Mean: 43.6	Years of migraine NR % with prior treatment Sodium Valproate: 65.2%
Oxcarbazepine	Silberstein, 2008[83] Sample 170 Analyzed 170 % of women 84.7	Migraine (International Headache Society) % without aura NR	Frequency of migraine headache per month (range, inclusion criteria): 3 to 9	16-65 Mean: 40.5	Years of migraine NR % with prior treatment NR
Gabapentin	Wessely, 1987[84] Sample 45 Analyzed 33 % of women 88.9	Common or classic migraine % without aura NR	Frequency of migraine headache per month: 5.23	NR Mean: 43	Years of migraine NR % with prior treatment NR
Gabapentin	Di Trapani, 2000[85] Sample 63 Analyzed 63 % of women 52.4	Migraine with or without aura according to the international Headache Society Classification of Headache % without aura 50.8	Frequency of migraine attack: 5.24	18-65 NR	Years of migraine NR % with prior treatment NR
Carbamazepine	Rompel, 1970[86] Sample NR Analyzed 48 % of women 68.8	"Typical Migraine" % without aura NR	Frequency of migraine attack: 2.97	NR (range: 14-60) NR	Years of migraine NR % with prior treatment NR
Lamotrigine	Steiner, 1997[87] Sample 77 Analyzed 77 % of women 81.8	Migraine (International Headache Society) % without aura 59.7	Frequency of migraine attack: 4.02	18-60 Mean: 37.2	Years of migraine NR (At least 2 years of recognizable attacks was required at entry) % with prior treatment NR

NR = not reported

Appendix Table D40. Funding and conflict of interest in randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Active drug	Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Acetazolamide	Vahedi, 2002[80]	Unclear (Funded from Association pour le Development des Neurosciences a Lariboisiere)	Yes	Yes	Not reported	All authors are employed in a hospital.
Gabapentin	Mathew, 2001[81]	Not reported	Yes	Yes	Not reported	Not reported
Vigabatrin	Ghose, 2002[82]	Industry	Yes	Yes	Not reported	Not reported
Oxcarbazepine	Silberstein, 2008[83]	Industry	Yes	Yes	Yes	S. Silberstein has received grants for other research or activities not reported in this article and has received honoraria during the course of this study from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year. J. Saper has received honoraria from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year, during the course of this study for other activities not reported in this article. F. Berenson has received honoraria from Novartis Pharmaceuticals Corporation, not in excess of US $10,000 per year, during the course of this study for other activities not reported in this article. M. Somogyi, K. McCague and J. D'Souza are employees of Novartis Pharmaceuticals Corporation.
Gabapentin	Wessely, 1987[84]	Not reported	Not reported	Not reported	Not reported	Not reported
Gabapentin	Di Trapani, 2000[85]	Not reported	Not reported	Yes	Not reported	Not reported
Carbamazepinee	Rompel, 1970[86]	Industry supplied the drugs.	Not reported	Not reported	Not reported	Not reported
Lamotrigine	Steiner, 1997[87]	Not reported	Yes	Yes	Not reported	Not reported

Appendix Table D41. Risk of bias in randomized controlled clinical trials that examined off label anti-epileptic drugs for migraine prevention in adults

Reference	Masking of Treatment Status	Planned Intention to Treat	Allocation Concealment	Adequacy of Randomization	Baseline Migraine Similarity	Selective Outcome Reporting	Risk of Bias
Vahedi, 2002[80]	DB	Yes	Yes	Yes	D	Unclear	Low
Mathew, 2001[81]	DB	Yes	Yes	No	F, S & D	Unclear	Medium
Ghose, 2002[82]	DB	No	Unclear	Not reported	F	Unclear	Medium
Silberstein, 2008[83]	DB	Yes	Yes	Yes	F, S & D (D: age at onset provided)	Unclear	Low
Wessely, 1987[84]	DB	No	Unclear	Not reported	Not reported	Unclear	Medium
Di Trapani, 2000[85]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Rompel, 1970[86]	DB	No	Unclear	Not reported	Not reported	Unclear	Medium
Steiner, 1997[87]	DB	Yes	Unclear	Not reported (No formal testing conducted, and no mention about the random adequacy)	Not reported (No formal testing conducted, and no mention about the random adequacy)	Unclear	Low

DB = double-blind
F = frequency
D = duration
S = severity

Appendix Table D42. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference Aim	Total Sample [Number Analyzed] % Females in Sample	Definition of Migraine	Duration of Migraine	Presence of Aura	Migraine Frequency at Baseline/Month	Age of Subjects (Mean or Median)
Ekbom, 1972[88] To investigate the effect of beta-receptor blocking agents on migraine by using a new compound, LB-46 (d,1-4-indol)	30 [26] 86.7	Ad Hoc Committee, 1962	Not reported	Since 4 had classic migraine it was assumed that these patients had migraine with aura	4	Mean 33.7 years
Sjaastad, 1972[89] To test the efficacy of Visken (LB-46) in migraine prophylaxis with a double-blind technique	28 [24] 85.7	Ad Hoc Committee on classification of headache (1962)	Not reported	Since 14 patients had classical migraine it was assumed that they had migraine with aura	2	Mean 35.8 years
Ekbom, 1975[90] Not reported	33 [28] 81.8	Ad Hoc Committee on classification of headache and World Federation of Neurology's Research Group on Migraine and Headache	Not reported	Since 6 patients had classic migraine it was assumed that these patients had migraine with aura	3	Mean 41.3 years
Nanda, 1978[91] Not reported	43 [33] 74.4	Migraine with the following characteristics: 1) Onset of first attack before age 25 years; 2) No evidence of a progressive neurological deficit over three years; 3) Hemicrania in association with any two of the following: a) family history, b) nausea and vomiting, and c) psychic, visual, or sensory prodroma	Not reported	Not reported	4.8	Not reported
Briggs, 1979[92] To assess the value of timolol in migraine prophylaxis and to elucidate further the reason for the varied response to different beta-blockers.	14 [Variable] 71.4	Ad Hoc Committee on classification of headache	Not reported	Since 2 patients had classical it was assumed that these patients had migraine with aura	2	Not reported

Appendix Table D42. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total Sample [Number Analyzed] % Females in Sample	Definition of Migraine	Duration of Migraine	Presence of Aura	Migraine Frequency at Baseline/Month	Age of Subjects (Mean or Median)
Ryan, 1982[93] Ryan, 1983[94] To determine the relative efficacy and safety of nadolol in reducing the frequency and/or the severity of migraine attacks as compared to placebo	80 [80] 77.5	Not reported	Not reported	Not reported	3	Not reported
Forssman, 1982[95] Forssman, 1983[96] To confirm the use of atenolol in migraine prophylaxis in a double-blind cross-over study with placebo	24 [20] 80.0	Ad Hoc Committee on classification of headache	Not reported	Since the definition of migraine was according to the Ad Hoc Committee classification it was assumed that none of the patients had aura	Not reported	Mean 40 years
Andersson, 1983[97] To evaluate whether metoprolol decreases 1) the frequency, 2) the severity of the migraine attacks, 3) days with migraine, 4) consumption of acute migraine medication, compared with placebo in patients with classical and non-classical migraine	71 [65] 84.5	Vahlquist's criteria and World Federation of Neurology Research Group on Migraine and Headache	18.4 years	Not reported	4.8	Mean 39.7 years
Stellar, 1984[79] To compare timolol with placebo	107 [94] 72.0	Ad Hoc Committee on Classification of Headache.	Not reported	Since 5 patients had classic migraine it was assumed that they had migraine with aura.	3	Mean 43 years
Freitag, 1984[98] To evaluate the efficacy of nadolol in reducing the frequency and severity of migraine headaches	32 [32] 81.3	Ad Hoc Committee on classification of headache	Not reported	Not reported	Not reported	Mean 36.3 years

Appendix Table D42. Randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total Sample [Number Analyzed] % Females in Sample	Definition of Migraine	Duration of Migraine	Presence of Aura	Migraine Frequency at Baseline/Month	Age of Subjects (Mean or Median)
Johannsson, 1987[99] To investigate the prophylactic anti-migraine effect of atenolol, a cardiovascular, water-soluble beta-antagonist	72 [63] 69.8	Ad Hoc Committee on classification of headache	26 years	Since the definition of migraine was according to the Ad Hoc Committee classification it was assumed that none of the patients had aura	2	Mean 43 years
Kangasneimi, 1987[100] To compare metoprolol with placebo in patients with frequent classic migraine attacks	77 [74] 79.7	NIH Ad Hoc Committee	17.2 years	Since all had classic migraine it was assumed all had migraine with aura	4.3	Mean 37.5 years
van de Ven, 1997[101] To assess the efficacy of bisoprolol in migraine prophylaxis	226 [Not reported] 82.0	Not reported	Age at onset (years): 20.3	23% of patients had migraine with aura and 77% migraine without aura	5.5	Mean 38.7 years
Siniatchkin, 2007[102] To investigate the influence of a controlled-release (CR) form of metoprolol on the amplitude and habituation of the early and late control negative variation (CNV) components using a double-blind, placebo-controlled, parallel-group design with systematic multiple CNV recordings during the treatment phase in order to provide more complete analysis of the treatment process.	20 [20] 85.0	International Headache Society criteria	22.3 years	One of the inclusion criteria was patients having migraine without aura	4.6	Mean 37 years

Appendix Table D43. Funding and conflict of interest in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference	Funding	Ethical Approval	Consensus	Conflict of Interest
Ekbom, 1972[88]	Not reported	Not reported	Not reported	Not reported
Sjaastad, 1972[89]	Not reported	Not reported	Not reported	Not reported
Ekbom, 1975[90]	Not reported (however, alprenolol was donated by AB Hassle, Gothenburg, Sweden)	Not reported	Not reported	Not reported
Nanda, 1978[91]	Grant	Not reported	Yes	Not reported
Briggs, 1979[92]	Not reported	Yes	Yes	Not reported
Ryan, 1982[93] Ryan, 1983[94]	Not reported	Not reported	Yes	Not reported
Forssman, 1982[95] Forssman, 1983[96]	Not reported	Not reported	Not reported	Not reported
Andersson, 1983[97]	Not reported	Yes	Yes	Not reported
Stellar, 1984[79]	Not reported	Not reported	Yes	Not reported
Freitag, 1984[98]	Not reported	Not reported	Yes	Not reported
Johannsson, 1987[99]	Not reported	Not reported	Not reported	Not reported
Kangasneimi, 1987[100]	Not reported	Yes	Yes	Not reported
van de Ven, 1997[101]	Industry	Yes	Yes	Not reported
Siniatchkin, 2007[102]	Not reported	Yes	Yes	Not reported

Appendix Table D44. Risk of bias in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Baseline Similarity	Selective Outcome Reporting	Risk of Bias
Ekbom, 1972[88]	Double-blind	No	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Medium
Sjaastad, 1972[89]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Ekbom, 1975[90]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Nanda, 1978[91]	Double-blind	No	Unclear	Not reported	Frequency: similar: Severity: not reported: Duration: not reported	Unclear	Medium
Briggs, 1979[92]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Ryan, 1982[93] Ryan, 1983[94]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Forssman, 1982[95] Forssman, 1983[96]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Andersson, 1983[97]	Double-blind	No	Unclear	Not reported. However, there were more males in metoprolol group (9/34 as compared to placebo group (2/37); the metoprolol group patients had more years of migraine (22.6 years) as compared to the placebo group (14.6 years)	The metoprolol group patients had more years of migraine (22.6 years) as compared to the placebo group (14.6 years). Frequency and severity of migraine were similar across the groups	Unclear	Medium
Stellar, 1984[79]	Double-blind	Yes	Unclear	Not adequate (The frequency of headaches with unilateral pain was significantly greater ($p<0.05$) in the timolol-placebo sequence group than in the placebo-timolol group	Frequency: similar; Severity: similar; Duration: similar	Unclear	Medium

Appendix Table D44. Risk of bias in randomized controlled clinical trials that examined efficacy of beta-blockers for migraine prevention in adults (continued)

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Baseline Similarity	Selective Outcome Reporting	Risk of Bias
Freitag, 1984[98]	Double-blind	Yes	Unclear	Not reported	Not reported	Unclear	Low
Johannsson, 1987[99]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Kangasneimi, 1987[100]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
van de Ven, 1997[101]	Double-blind	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Medium
Siniatchkin, 2007[102]	Double-blind	No	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Medium

Appendix Table D45. Strength of evidence of migraine prevention with beta-blockers in adults (sorted by drug name)

Definition of the Outcome	Drug Name	Reference	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Better during the period of the trial	Acebutolol	Nanda, 1978[91]	Medium	Yes	Not applicable	Yes	Low
Better during the period of the trial	Alprenolol	Ekbom, 1975[90]	Medium	Yes	Not applicable	No	Low
Reduction of integrated headache more than 50%	Atenolol	Forssman, 1982[95] Forssman, 1983[96]	Medium	Yes	Not applicable	Yes	Low
Reduction of number of attacks more than 50%	Atenolol	Forssman, 1982[95] Forssman, 1983[96]	Medium	Yes	Not applicable	Yes	Low
Consumption of ergotamine drugs	Atenolol	Forssman, 1982[95] Forssman, 1983[96]	Medium	Yes	Not applicable	Yes	Low
Patients' subjective judgment of their migraine: complete remission/marked improvement	Metoprolol	Kangasneimi, 1987[100]	Medium				
Effect: marked or moderate	Metoprolol	Andersson, 1983[97]	Medium				
Pooled	Metoprolol		Medium	Yes	Yes	No	Low
Patients' subjective judgment of their migraine: Medium improvement	Metoprolol	Kangasneimi, 1987[100]	Medium	Yes	Not applicable	No	Low
Effect: slight	Metoprolol	Andersson, 1983[97]	Medium	Yes	Not applicable	No	Low
Treatment successful: Frequency	Nadolol	Freitag, 1984[98]	Low	Yes	Not applicable	No	Low
Treatment successful: Intensity	Nadolol	Freitag, 1984[98]	Low	Yes	Not applicable	No	Low
Treatment successful: Pain	Nadolol	Freitag, 1984[98]	Low	Yes	Not applicable	No	Low
Treatment successful: Relief	Nadolol	Freitag, 1984[98]	Low	Yes	Not applicable	No	Low
Completely relieved of migraine	Timolol	Briggs, 1979[92]	Medium	Yes	Not applicable		Low
Responders (Patients with 50% or greater reduction in headache frequency)	Timolol	Stellar, 1984[79]	Medium	Yes	Not applicable	No	Low
Global response of great or moderate improvement: to only one therapy	Timolol	Stellar, 1984[79]	Medium	Yes	Not applicable	No	Low
Patient rating of medication as extremely or moderately helpful: to only one therapy	Timolol	Stellar, 1984[79]	Medium	Yes	Not applicable	No	Low
Headaches with nausea: frequency per 28 days	Timolol	Stellar, 1984[79]	Medium	Yes	Not applicable	No	Low

Appendix Table D46. Efficacy of beta-blockers in prevention of migraine in adults; results from randomized controlled clinical trials (sorted by drug name)

Reference Risk of Bias	Drug and Dose	Outcome	Events/ Randomized [Rate of Outcome with Drug, %]	Events/ Randomized [Rate of Outcome with Placebo, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1000 Treated (95% CI)
Ekbom, 1975[90] Medium	Alprenolol 200mg/day ("Durules")	Better during the period of the trial	11/33 [33.3%]	12/33 [36.4%]	0.9 (0.5 to 1.8)	-0.03 (-0.26 to 0.2)		
Forssman, 1982[95] Forssman, 1983[96] Medium	**Atenolol 100mg/day**	**Reduction of integrated headache more than 50%**	**11/24 [45.8%]**	**0/24 [0.0%]**	**23.0 (1.4 to 369.5)**	**0.46 (0.26 to 0.7)**	**2 (2 to 4)**	**458 (255 to 661)**
Forssman, 1982[95] Forssman, 1983[96] Medium	**Atenolol 100mg/day**	**Reduction of number of attacks more than 50%**	**8/24 [33.3%]**	**0/24 [0.0%]**	**17.0 (1.0 to 278.9)**	**0.33 (0.14 to 0.5)**	**3 (2 to 7)**	**333 (140 to 527)**
Forssman, 1982[95] Forssman, 1983[96] Medium	**Atenolol 100mg/day**	**Consumption of ergotamine drugs**	**14/24 [58.3%]**	**0/24 [0.0%]**	**29.0 (1.8 to 460.1)**	**0.58 (0.38 to 0.8)**	**2 (1 to 3)**	**583 (382 to 784)**
Kangasneimi, 1987[100] Medium	**Metoprolol 200mg once daily ("Durules")**	**Patients' evaluation: complete remission/marked improvement**	**29/77 [38.0%]**	**16/77 [21.0%]**	**1.8 (1.1 to 3.1)**	**0.17 (0.03 to 0.3)**	**6 (3 to 36)**	**169 (28 to 310)**
Andersson, 1983[97] Medium	**Metoprolol 200mg once daily ("Durules")**	**Patients' evaluation: complete remission/marked improvement**	**15/34 [44.1%]**	**6/37 [16.2%]**	**2.7 (1.2 to 6.2)**	**0.28 (0.07 to 0.5)**	**4 (2 to 13)**	**279 (74 to 484)**
		Pooled[97,100]	**44/111 [39.9%]**	**22/114 [19.4%]**	**2.0 (1.3 to 3.2)**	**0.20 (0.09 to 0.3)**	**5 (3 to 11)**	**204 (88 to 321)**
		Heterogeneity			P value = 0.42 I squared = 0%	P value = 0.39 I squared = 0%		
Kangasneimi, 1987[100] Medium	Metoprolol 200mg once daily ("Durules")	Patients' subjective judgment of their migraine: moderate improvement	14/77 [18.0%]	15/77 [19.0%]	0.9 (0.5 to 1.8)	-0.01 (-0.14 to 0.1)		
Andersson, 1983[97] Medium	Metoprolol 200mg once daily ("Durules")	Patients' subjective judgment of their migraine: slight	7/34 [20.6%]	10/37 [27.0%]	0.8 (0.3 to 1.8)	-0.06 (-0.26 to 0.1)		

Appendix Table D46. Efficacy of beta-blockers in prevention of migraine in adults; results from randomized controlled clinical trials (sorted by drug name) (continued)

Reference Risk of Bias	Drug and Dose	Outcome	Events/ Randomized [Rate of Outcome with Drug, %]	Events/ Randomized [Rate of Outcome with Placebo, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1000 Treated (95% CI)
Freitag, 1984[98] Low	**Nadolol 80mg to 240mg/day**	**Treatment successful: Frequency**	**6/24 [25.0%]**	**0/8 [0.0%]**	**4.7 (0.3 to 75.0)**	**0.25 (0.02 to 0.5)**	**4 (2 to 45)**	**250 (22 to 478)**
	Nadolol 80mg to 240mg/day	**Treatment successful: Intensity**	**7/24 [29.2%]**	**0/8 [0.0%]**	**5.4 (0.3 to 85.3)**	**0.29 (0.06 to 0.5)**	**3 (2 to 17)**	**292 (58 to 525)**
	Nadolol 80mg to 240mg/day	**Treatment successful: Pain**	**7/24 [29.2%]**	**0/8 [0.0%]**	**5.4 (0.3 to 85.3)**	**0.29 (0.06 to 0.5)**	**3 (2 to 17)**	**292 (58 to 525)**
	Nadolol 80mg to 240mg/day	**Treatment successful: Relief**	**10/24 [41.7%]**	**0/8 [0.0%]**	**7.6 (0.5 to 116.2)**	**0.42 (0.17 to 0.7)**	**2 (2 to 6)**	**417 (172 to 661)**
Briggs, 1979[92] Medium	Timolol 10mg twice a day	Completely relieved of migraine	2/14 [14.3%]	0/14 [0.0%]	5.0 (0.3 to 95.6)	0.14 (-0.07 to 0.4)		
Stellar, 1984[79] Medium	**Timolol 10mg twice a day**	**Responders (Patients with 50% or greater reduction in headache frequency)**	**25/47 [53.2%]**	**10/47 [21.3%]**	**2.5 (1.4 to 4.6)**	**0.32 (0.13 to 0.5)**	**3 (2 to 7)**	**319 (135 to 504)**
	Timolol 10mg twice a day	**Global response of great or moderate improvement**	**35/47 [74.5%]**	**12/47 [25.5%]**	**2.9 (1.7 to 4.9)**	**0.49 (0.31 to 0.7)**	**2 (2 to 3)**	**489 (313 to 666)**
	Timolol 10mg twice a day	**Patient rating of medication as extremely or moderately helpful**	**32/47 [68.1%]**	**12/47 [25.5%]**	**2.7 (1.6 to 4.5)**	**0.43 (0.24 to 0.6)**	**2 (2 to 4)**	**426 (243 to 608)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D47. Efficacy of beta-blockers for migraine prevention in adults on intermediate outcomes of migraine frequency, duration, and severity (results from randomized controlled clinical trials) (sorted by drug name)

Reference Risk of Bias	Drug, Dose	Outcome	Randomized into Drug/Placebo Groups	Mean Difference (95% CI)
Ekbom, 1975[90] Medium	Alprenolol 200mg/day ("Durules")	Migraine attacks per week	33/33	0.2 (-0.9 to 1.3)
	Alprenolol 200mg/day ("Durules")	Headache index per week	33/33	0.2 (-1.7 to 2.1)
Kangasneimi, 1987[100] Medium	Metoprolol 200mg once daily ("Durules")	Day with migraine per 4 weeks	77/77	0.7 (0.1 to 1.1)
Andersson, 1983[97] Medium	**Metoprolol 200mg once daily ("Durules")**	**Mean number of migraine days**	**34/37**	**-2.1 (-3.8 to -0.5)**
Kangasneimi, 1987[100] Medium	Metoprolol 200mg once daily ("Durules")	Day with migraine per 4 weeks: aura attacks	77/77	0.8 (0.0 to 0.7)
	Metoprolol 200mg once daily ("Durules")	**Mean duration (h) per attack: total**	**77/77**	**2.0 (0.2 to 2.9)**
	Metoprolol 200mg once daily ("Durules")	Mean duration (h) per attack: aura attacks	77/77	1.3 (-0.3 to 2.5)
	Metoprolol 200mg once daily ("Durules")	Attack frequency per 4 weeks: total	77/77	0.7 (0.2 to 1.0)
Andersson, 1983[97] Medium	Metoprolol 200mg once daily ("Durules")	Mean attack frequency	34/37	-1.5 (-2.4 to -0.6)
Siniatchkin, 2007[102] Medium	Metoprolol 200mg once daily ("Durules")	Frequency of migraine attacks	10/10	-0.9 (-2.2 to 0.4)
			Pooled[97, 102]	-0.5 (-2.1 to 1.1)
Kangasneimi, 1987[100] Medium	**Metoprolol 200mg once daily ("Durules")**	**Attack frequency per 4 weeks: aura attacks**	**77/77**	**0.6 (0.1 to 0.6)**
	Metoprolol 200mg once daily ("Durules")	**Sum of intensity score per 4 weeks: total**	**77/77**	**0.9 (0.7 to 2.4)**
	Metoprolol 200mg once daily ("Durules")	**Sum of intensity score per 4 weeks: aura attacks**	**77/77**	**1.2 (0.3 to 1.8)**
	Metoprolol 200mg once daily ("Durules")	**Mean intensity score per attack: total**	**77/77**	**0.1 (0.1 to 0.4)**
	Metoprolol 200mg once daily ("Durules")	Mean intensity score per attack: aura attacks	77/77	0.0 (-0.1 to 0.4)
Andersson, 1983[97] Medium	**Metoprolol 200mg once daily ("Durules")**	**Sum of severity score (migraine days' intensity) 1=Annoying, but patient not disabled; 2=Patient pertly disabled (affecting his/her ability to work); and 3=Patient disabled -unable to work or in bed)**	**34/37**	**-4.6 (-8.2 to -0.9)**

Appendix Table D47. Efficacy of beta-blockers for migraine prevention in adults on intermediate outcomes of migraine frequency, duration, and severity (results from randomized controlled clinical trials) (sorted by drug name) (continued)

Reference Risk of Bias	Drug, Dose	Outcome	Randomized into Drug/Placebo Groups	Mean Difference (95% CI)
Kangasneimi, 1987[100] Medium	**Metoprolol 200mg once daily ("Durules")**	**Sum of global ratings per 4 weeks: total**	**77/77**	**4.1 (1.3 to 6.4)**
	Metoprolol 200mg once daily ("Durules")	**Sum of global ratings per 4 weeks: aura attacks**	**77/77**	**3.6 (0.7 to 5.5)**
	Metoprolol 200mg once daily ("Durules")	**Mean global rating (1-10) per attack: total**	**77/77**	**1.0 (0.2 to 1.3)**
	Metoprolol 200mg once daily ("Durules")	**Mean global rating (1-10) per attack: aura attacks**	**77/77**	**0.6 (0.2 to 1.5)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per 4 weeks: aura attacks**	**77/77**	**0.8 (0.2 to 2.9)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per attack: total**	**77/77**	**1.0 (0.2 to 1.0)**
	Metoprolol 200mg once daily ("Durules")	**Consumption of analgesic tablets per attack: aura attack**	**77/77**	**0.5 (0.1 to 0.8)**
	Metoprolol 200mg once daily ("Durules")	Consumption of ergotamine tablets per 4 weeks: total	77/77	1.5 (0.0 to 2.1)
	Metoprolol 200mg once daily ("Durules")	Consumption of ergotamine tablets per 4 weeks: aura attacks	77/77	1.5 (-0.4 to 1.4)
Andersson, 1983[97] Medium	**Metoprolol 200mg once daily ("Durules")**	**Acute tablet consumption**	**34/37**	**-9.3 (-16.4 to -2.2)**
Kangasneimi, 1987[100] Medium	**Metoprolol 200mg once daily ("Durules")**	**Consumption of analgesic tablets per 4 weeks**	**77/77**	**2.5 (0.5 to 4.8)**
			Pooled[97,100]	-2.9 (-14.5 to 8.6)
Sjaastad, 1972[89] Medium	Pindolol (LB-46) 7.5 to 15mg	Headache days	28/28	0.5 (-2.3 to 3.4)
	Pindolol (LB-46) 7.5 to 15mg	Headache indices	28/28	-0.1 (-4.5 to 4.3)
Briggs, 1979[92] Medium	Timolol 10mg twice a day	Headache frequency	14/14	1.6 (-1.2 to 4.4)
	Timolol 10mg twice a day	**Headache frequency**	**14/14**	**3.1 (0.2 to 5.9)**

Bold = significant differences at 95% confidence limit when 95%CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D48. Efficacy of beta-blockers on migraine severity in adults; results from randomized controlled clinical trials (sorted by drug name)

Reference Risk of Bias	Drug and Dose	Outcome	Events/ Randomized [Rate of Outcome with Drug, %]	Events/ Randomized [Rate of Outcome with Placebo, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1000 Treated (95% CI)
Andersson, 1983[97] Medium	**Metoprolol 200mg/day**	**50% reduction in sum of severity score**	**10/34 [29.4%]**	**4/37 [10.8%]**	**2.7 (0.9 to 7.9)**	**0.19 (0.00 to 0.4)**	**5 (3 to 326)**	**186 (3 to 369)**
	Metoprolol 200mg/day	**1-50% reduction in the sum of severity score**	**15/34 [44.1%]**	**8/37 [21.6%]**	**2.0 (1.0 to 4.2)**	**0.22 (0.01 to 0.4)**	**4 (2 to 85)**	**225 (12 to 438)**
Sjaastad, 1972[89] Medium	Pindolol 7.5 to 15mg	50% reduction in headache indices	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)		

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D49. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults

Examined Drug	Reference, Total Sample Size Number of Analyzed % Women	Definition of Migraine % of Patients without Aura	Baseline Monthly Migraine Frequency	Eligible Age Mean Age of Subjects	Duration of Migraine Prior Treatment
Amitriptyline	Couch, 1979[103] Sample 116 Analyzed 100 % women 84	Modified 1962 Ad Hoc National Institutes of Health Committee NR	NR	15-60 NR	NR NR
Amitriptyline	Gomersall, 1973[104] Sample 26 Analyzed 20 % women 75	Ad hoc committee NR	NR	NR 21-30 years old:1 31-40 years old:4 41-50 years old:11 51-60 years old:2 61-70 years old:2	1-10 yr:5 11-20 yr:5 21-30 yr:6 31-40:2 41-50:2 NR
Amitriptyline	Mathew, 1981[105] Sample 715 Analyzed 554 % women 94.5	NR NR	NR	NR (age ranged from 19-57) Mean: 38	NR NR
Amitriptyline	Bank, 1994[106] Sample 64 Analyzed 51 % women 73.4	International Headache Society 81.25	Headache Unit Index active group = 0.16, Headache Unit Index control group = 0.24	NR 34	At least 12 months NR
Amitriptyline	Oguzhanoglu, 1999[107] Sample 17 Analyzed 15 % women 80	International Headache Society NR	NR	NR 31	NR NR
Amitriptyline	Krymchantowski, 2002[108] Sample 39 Analyzed 27 % women 66.7	NR NR	NR	NR 36.4	NR 100% overusing symptomatic medications
Amitriptyline	Bulut, 2004[109] Sample 76 Analyzed 52 % women 84.6	International Headache Society 77	Yes	16-50 31.9	NR NR
Amitriptyline	Lampl, 2009[110] Sample 132 Analyzed 132 % women 73	International Headache Society 76	Yes	18-60 32	16 years NR

Appendix Table D49. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults (continued)

Examined Drug	Reference, Total Sample Size Number of Analyzed % Women	Definition of Migraine % of Patients without Aura	Baseline Monthly Migraine Frequency	Eligible Age Mean Age of Subjects	Duration of Migraine Prior Treatment
Amitriptyline	Couch, 2011[111] Sample 391 Analyzed 317 % women 81	Modified 1962 Ad Hoc National Institutes of Health Committee NR	NR	18-70 34.9	NR NR
Amitriptyline	Couch, 1976[112] Sample 114 Analyzed 73 % women 84.9	Not specified NR	NR	NR NR	NR NR
Amitriptyline	Rafieian-Kopaei, 2005[64] Sample 105 Analyzed 95 % women NR	International Headache Society NR	Mean attack frequency: 4.02 (per month)	Adolescent & Adults NR	>1 (from inclusion criteria) NR
Amitriptyline	Rafieian-Kopaei, 2005[64] Sample 105 Analyzed 95 % women NR	International Headache Society NR	4.02 migraine attacks per month, 25.12 h average duration	15-45 NR	At least 12 months NR
Femoxetine	Orholm, 1986[113] Sample 65 Analyzed 53 % women 84.9	Paroxysmal headache associated with discomfort, possibly with inability to work, and at least one of the following symptoms: nausea, vomiting, visual disturbances and paresthesia NR	Yes	NR ≥50 years old = 12 30-50 years old = 38 <30 years old = 3	NR NR
Femoxetine	Zeeberg, 1981[114] Sample 59 Analyzed 45 % women 86.7	Paroxysmal headache associated with discomfort, possibly with inability to work, and at least one of the following symptoms: nausea, vomiting, visual disturbances and paresthesia NR	Yes	NR ≥50 years old = 9 30-50 years old = 29 <30 years old = 7	NR NR
Femoxetine	Kangasniemi, 1983[77] Sample 29 Analyzed 24 % women 86.2	NR NR	Yes	NR 37	NR NR

Appendix Table D49. Randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults (continued)

Examined Drug	Reference, Total Sample Size Number of Analyzed % Women	Definition of Migraine % of Patients without Aura	Baseline Monthly Migraine Frequency	Eligible Age Mean Age of Subjects	Duration of Migraine Prior Treatment
Femoxetine	Orholm, 1985[115] Sample 59 Analyzed 47 % women NR	NR NR	NR	NR NR	NR NR
Fluoxetine	Adly, 1992[116] Sample 32 Analyzed 18 % women 83.3	the Ad hoc Committee on Classification of headache NR	Headache score 33.5	NR 37.5	NR 2 amitriptyline or nadolol, 1 imipramine
Fluoxetine	Saper, 1994[117] Sample 111 Analyzed 111 % women 87.4	International Headache Society NR	NR	18-60 36.6	At least 24 months NR
Fluoxetine	Steiner, 1998[118] Sample 53 Analyzed 49 % women 75.5	NR 54.8	Yes	18-45 40.6	NR NR
Fluoxetine	d'Amato, 1999[119] Sample 52 Analyzed 52 % women 63.5	International Headache Society 1988 criteria 100	NR	18-65 37.6	At least 6 months NR
Mianserin	Monro, 1985[120] Sample 38 Analyzed 34 % women NR	NR NR	NR	18-65 NR	NR NR
Tonabersat*	Goadsby, 2009[121] Sample 124 Analyzed 124 % women 92.3	International Headache Society NR	Yes	18-55 36	NR NR
Venlafaxine	Ozyalcin, 2005[122] Sample 60 Analyzed 49 % women 90	International Headache Society 100	Yes	18-70 placebo 38.16; V75 34.25; V150 37.19	NR NR
Venlafaxine	Tarlaci, 2009[123] Sample 105 Analyzed 93 % women 81.7	International Headache Society 93.5	Yes	NR 31.4	NR NR

NR = not reported; *Cortical spreading depression inhibitor

Appendix Table D50. Funding and conflict of interest in randomized controlled clinical trials that examined off label antidepressants for migraine prevention in adults

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Couch, 1979[103]	Industry	No	Yes	NR	NA
Gomersall, 1973[104]	Industry	No	Yes	NR	NA
Mathew, 1981[105]	NR	NR	NR	NR	NR
Bank, 1994[106]	NR	No	Yes	NR	NA
Oguzhanoglu, 1999[107]	NR	No	NR	NR	NA
Krymchantowski, 2002[108]	No	No	Yes	NR	NA
Bulut, 2004[109]	Industry	Yes	Yes	NR	NA
Lampl, 2009[110]	No	Yes	Yes	Yes	Dr. Lampl received personal compensation from Glaxo, Pfizer Austria, Mundipharma, Gru¨ nenthal, Bayer-Shering, Biogen Idec and Astra Zeneca
Couch, 2011[111]	Industry	Yes	Yes	NR	NA
Couch, 1976[112]	No	No	NR	NR	NA
Rafieian-Kopaei, 2005[64]	Other	NR	Yes	NR	All authors are from the University that sponsored the study
Rafien-Kopaei, 2005[64]	University	No	Yes	NR	NA
Orholm, 1986[113]	No	Yes	Yes	NR	NA
Zeeberg, 1981[114]	No	Yes	Yes	NR	NA
Kangasniemi, 1983[77]	No	No	NR	NR	NA
Orholm, 1985[115]	NR	NR	NR	NR	NA
Adly, 1992[116]	NR	No	Yes	NR	NA
Saper, 1994[117]	Industry	Yes	Yes	NR	NA
Steiner, 1998[118]	Industry	Yes	Yes	NR	NA
d'Amato, 1999[119]	NR	Yes	Yes	NR	NA
Monro, 1985[120]	Industry	No	Yes	NR	NA
Goadsby, 2009[121]*	Industry	No	Yes	NR	JGM is an employee of Minster Research Ltd
Ozyalcin, 2005[122]	Industry	Yes	Yes	NR	NA
Tarlaci, 2009[123]	No	No	NR	NR	NA

NA = Not applicable; NR = Not reported; * RCT of Cortical spreading depression inhibitor

Appendix Table D51. Risk of bias in randomized controlled clinical trials that examined off label antidepressants and tonabersat for migraine prevention in adults

Reference	Masking of Treatment Status	Planned Intention to Treat Analysis	Allocation Concealment	Adequacy of Randomization	Adequacy of Randomization (Migraine Characteristics)	Selective Outcome Reporting	Risk of Bias
Couch, 1979[103]	DB	No	NR	Yes	Unclear	Unclear	Medium
Gomersall, 1973[104]	DB	No	Unclear	Unclear (crossover trial)	Unclear (crossover trial)	Unclear	Medium
Mathew, 1981[105]	Open-label	No	Unclear	Yes	NR	Unclear	High
Bank, 1994[106]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Oguzhanoglu, 1999[107]	Open-label	No	Unclear	Unclear	F & S	Unclear	Medium
Krymchantowski, 2002[108]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Bulutm 2004[109]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Lampl, 2009[110]	Open-label	Yes	NR	Yes	F & S	Unclear	Medium
Couch, 2011[111]	DB	No	NR	Yes	F & S	Unclear	Medium
Couch, 1976[112]	DB	No	Unclear	NR	NR	Unclear	Medium
Rafieian-Kopaei, 2005[64]	DB	No	Unclear	NR	F	Unclear	Medium
Rafieian-Kopaei, 2005[64]	DB	No	NR	Unclear	S	Unclear	Medium
Orholm, 1986[113]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Zeeberg, 1981[114]	DB	No	Unclear	Yes	F & S	Unclear	Medium
Kangasniemi, 1983[77]	DB	No	Unclear	NR	NR	Unclear	Medium
Orholm, 1985[115]	DB	No	NR	Yes	F & S	Unclear	Medium
Adly, 1992[116]	DB	No	Unclear	Yes	S	Unclear	Medium
Saper, 1994[117]	DB	No	NR	Yes	S	Unclear	Medium
Steiner, 1998[118]	DB	No	NR	No	No for F, but S is OK	Unclear	High
d'Amato, 1999[119]	DB	No	NR	Yes	S	Unclear	Medium
Monro, 1985[120]	DB	No	Unclear	No	Unclear	Unclear	High
Goadsby, 2009[121]*	DB	Yes	NR	Yes	F & S	Unclear	Low
Ozyalcin, 2005[122]	DB	No	Unclear	Yes	Unclear	Unclear	Medium
Tarlaci, 2009[123]	NR (seems open-label)	Yes	NR	No	F	Unclear	High

DB = double–blind
NR = not reported
F = migraine frequency
S = migraine severity
D = migraine duration
***** RCT of Cortical spreading depression inhibitor

Appendix Table D52. Randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference Sample Analyzed % Women	Definition of Migraine Years of Migraine	Age of Subjects	Baseline Migraine Status
Markley, 1984[124] Sample 20 Analyzed 14 % women 86	"Standard criteria" confirmed by self assessment questionnaire Years of migraine- Chronic headaches for an average of 13.4 years	20 to 50 year Mean age 33 years	57% had no significant relief when treated in the past with drugs used for migraine prophylaxis
Stewart, 1988[125] Sample 49 Analyzed 26 % women not reported	Not reported Years of migraine not reported	18-65	Headache index at baseline: active=126.7 (SD=112.5), placebo=141.1 (SD=142.3); number of headaches at baseline: active=6.15 (SD+3.62), placebo=6.46 (SD=4.21)
Leandri, 1990[126] Sample 30 Analyzed 30 % women 73	International Headache Society criteria Years of migraine, mean: 7.9 +/- 6.2 years	Not reported Not reported	Mean frequency ± SD: 4.26 ± 3.03, mean intensity: 2.60 ± 0.49, mean duration: 35.76 ± 21.69, index a (monthly number x mean intensity of attacks): 12.61 ±10.96, index b (monthly number x mean intensity x mean duration of attacks): 351.88 ± 214.84
Gelmers, 1983[127] Sample 60 Analyzed 50 % women 62	Ad Hoc Committee definition Years of migraine- 20 years	Not reported Mean (SD): 30 (9)	Classic migraine active: 8, class migraine placebo: 4, common migraine active: 20, common migraine placebo: 18, age at migraine onset active: 11 (SD=9), age at migraine onset placebo: 10 (SD=8), migraine index active: 56 (SD=25), migraine index placebo: 72 (SD=39)
Migraine-Nimodipine European Study Group, 1989[128] Sample 192 Analyzed 192 % women 78	Ad hoc committee definition Years of migraine, active: 16, placebo 17	Age 18-60 Mean: active 38, placebo 38.3 years	Median duration of migraine in years, active: 16, placebo: 17; migraine days per 4 weeks, active: 4.5, placebo: 4.2; migraine index of days per 4 weeks times severity, active: 9.27, placebo 8.79
McArthur, 1989[129] Sample 24 Analyzed 14 % women Not reported	Ad hoc committee on the classification of headache Years of migraine Not reported	Not reported Not reported	Not reported
Solomon, 1983[130] Sample 23 Analyzed 12 % women 75	Classic or common migraine by ad hoc committee on classification of headache Years of migraine Not reported	Age 19-60 Mean 38.9 years	7/12 (58%) had common migraine and 5/12 (42%) had classic migraine

Appendix Table D52. Randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults (continued)

Reference Sample Analyzed % Women	Definition of Migraine Years of Migraine	Age of Subjects	Baseline Migraine Status
Meyer, 1983[131] Sample 35 Analyzed 35 % women 66	Ad hoc committee Years of migraine Not reported	Age 20 years and older Mean 39.6 (SD=12.1) years	27/35 (77%) patients with migraine, common migraine: 14/35 (40%), classic migraine: 13/35 (37%), cluster headaches: 8/35 (23%)
Havanka-Kanniainen, 1985[132] Sample 33 Analyzed 29 % women 85	Ad hoc committee Years of migraine- Mean duration of 14 years (1.6)	Not reported Mean age 32 (SD=1.3)	20/30 (67%) with classical migraine, 33% with common,
Migraine-Nimodipine European Study Group, 1989[133] Sample 89 Analyzed 72 % women 79	National Institute of Health for classic migraine Years of migraine- Active: 15 years, control: 10 years	18-60 Mean age active: 33.2 yrs., control: 34.8 yrs.	Migraine days/4 weeks active: 3.4, control: 3.4; migraine index active: 7.7, control: 8.1
Ansell, 1988[134] Sample 68 Analyzed 57 % women 71	Defined in accordance with the definition of the research group on migraine and headache of the world federation of neurology, 1969 Years of migraine- Not reported	18-60 Not reported	Placebo group: 16 common migraine, 11 classical migraine; active group: 14 with common migraine and 14 with classical migraine
Shukla, 1995[135] Sample 36 Analyzed 28 % women 79	International Headache Society Years of migraine- 8.8 (1.18) years	15-45 Mean years: 29.8 (SD=1.89)	Frequency: 10.4 (1.76), mild severity 0/28, moderate severity 12/28, severe severity 16/28, 100% with nausea/vomiting

Appendix Table D53. Funding and conflict of interest in randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference	Sponsorship	Ethical Approval of Study	Consent of Participants	Conflict of Interest
Markley, 1984[124]	Industry (Knoll Pharmaceutical) provided medication	Not reported	Yes	Not reported
Leandri, 1990[126]	Industry (Sandoz Prodotti Farmaceutici supplied medications)	Not reported	Yes	Not reported
Stewart, 1988[125]	Not reported	Not reported	Yes	Not reported
Gelmers, 1983[127]	Not reported	Not reported	Yes	Not reported
Migraine-Nimodipine European Study Group, 1989[128]	Not reported	Not reported	Not reported	Not reported
McArthur, 1989[129]	Industry (Pfizer) and not for profit (national migraine foundations)	Not reported	Yes	Not reported
Solomon, 1983[130]	Industry (Knoll Pharmaceutical) provided medication	Not reported	Yes	Not reported
Meyer, 1983[131]	Grant from government	Yes	Yes	Not reported
Havanka-Kanniainen, 1985[132]	Industry (Bayer Ltd supplied medications)	Yes	Yes	Not reported
Migraine-Nimodipine European Study Group, 1989[133]	Not reported	Not reported	Not reported	Not reported
Ansell, 1988[134]	Not reported	Not reported	Yes	Not reported
Shukla, 1995[135]	Not reported	Not reported	Yes	Not reported

Appendix Table D54. Risk of bias in randomized controlled clinical trials that examined calcium channel antagonists for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Markley, 1984[124]	Double blind	No	Unclear	Not reported	No	Medium
Stewart, 1988[125]	Double blind	No	Unclear	Unclear	Unclear	Medium
Leandri, 1990[126]	Double blind	No	Unclear	Yes	No	Medium
Gelmers, 1983[127]	Double blind	No	Unclear	Yes	No	Medium
Migraine-Nimodipine European Study Group, 1989[128]	Double blind	Yes	Unclear	No, migraine index different between nimodipine and placebo groups	No	Medium
McArthur, 1989[129]	Double blind	No	Unclear	No, migraine index different between nimodipine and placebo groups	No	High
Solomon, 1983[130]	Double blind	No	Unclear	Unclear	No	Medium
Meyer, 1983[131]	Double blind	No	Unclear	Unclear	No	Medium
Havanka-Kanniainen, 1985[132]	Double blind	No	Unclear	Unclear	No	Medium
Migraine-Nimodipine European Study Group, 1989[133]	Double blind	Yes	Unclear	Yes	No	Low
Ansell, 1988[134]	Double blind	No	Unclear	Unclear, more classical migraine in active group	No	Medium
Shukla, 1995[135]	Double blind	No	Unclear	Unclear	No	Medium

Appendix Table D55. Randomized controlled clinical trials that examined ACE inhibitors of Angiotensin II receptor blockers for migraine prevention in adults

Active Drug	Reference Sample Analyzed % Women	Definition of Migraine Years of Migraine	Eligible Age of Subjects	Baseline Migraine Status
Lisinopril	Schrader, 2001[136] Sample 60 Analyzed 55 % women 81	International Headache Society criteria Years of migraine Not reported	Age 18 to 60 years gender, mean (SD): women, 41 (9), men, 43 (5) years	Mean (SD); hours with headache: 65(74), days with headache 9.4(4.0), days with migraine 6.8(3.0)
Captopril	Minervini, 1987[137] Sample 12 Analyzed 12 % women 58	Ad Hoc committee on the classification of headache Years of migraine 7-36 years	Not reported 35-64	Not reported
Candesartan	Tonvik, 2003[138] Sample 60 Analyzed 57 % women 79	International Headache Society criteria Years of migraine Not reported	Age 18 to 65 years mean (SD) women: 42(11), men: 48(12)	Mean (SD) of Migraine days 5.7 (2.9) Disability level 9.7 (6.4) Sick leave days 1.00 (2.00)
Telmisartan	Diener, 2009[139] Sample 84 Analyzed 84 % women 84.5	International Headache Society criteria Years of migraine Not reported	18-65 Active group: 39.8 (11.7), placebo: 41.6 (12.9) years	Migraine days active: 6.2 (SD=2.9), placebo: 7.6 (SD=3.7); headache hours active: 58.2 (SD=50.4), placebo: 74.4 (SD=64.2)

Appendix Table D56. Funding and conflict of interest in randomized controlled clinical trials that examined ACE inhibitors of Angiotensin II receptor blockers for migraine prevention in adults

Reference	Sponsorship	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Disclosed Relationships
Schrader, 2001[136]	Industry by AstraZeneca	Yes	Yes	Yes	HS and GB have been reimbursed by AstraZeneca, one of the manufacturers of lisinopril, for attending conferences. These conferences were unrelated to the present study.
Minervini, 1987[137]	Not reported	Not reported	Not reported	Not reported	Not applicable
Tronvik, 2003[138]	Industry by AstraZeneca	Yes	Yes	Yes	Dr. Tronvik has been reimbursed by AstraZeneca for attending a conference unrelated to the present study.
Diener, 2009[139]	By industry (Boehringer Ingelheim)	Yes	Yes	Yes	Multiple authors with honoraria or past research funding with pharmaceutical industry

Appendix Table D57. Risk of bias in randomized controlled clinical trials that examined ACE inhibitors of Angiotensin II receptor blockers for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Schrader, 2001[136]	Double blind	Yes	Adequate	Not reported	No	Low
Minervini, 1987[137]	Double blind	Unclear	Unclear	Unclear	No	Low
Tronvik, 2003[138]	Double blind	Yes	Adequate	Not reported	No	Low
Diener, 2009[139]	Double blind	No	Unclear	Headache hours greater in placebo group at baseline	No	High

Appendix Table D58. Randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference Sample Analyzed % Women	Definition of Migraine Years of Migraine	Eligible Age of Subjects	Baseline Migraine Status
Ryan, 1975[140] Sample 75 Analyzed 75 % women 80	Common or classical migraine Years of migraine Not reported	21-60 Not reported	17 tyramine positive, 58 tyramine negative
Ryan, 1975[141] Sample 133 Analyzed 133 % women 78	Not reported Years of migraine: Median duration 22 years	Not reported Median age 41 years	4/133 (3%) had migraine related to menses, 32/133 (24%) had migraine related to emotional stress
Shafar, 1972[142] Sample 65 Analyzed 50 % women 84	Not reported Years of migraine: Not reported	Not reported Median age females=48 years, median age males=45 years	Not reported
Stensrud, 1976[143] Sample 29 Analyzed 27 % women 83	Not reported Years of migraine: Not reported	Not reported Mean 45.4 years	Mean number of headache days at baseline: 5.78, mean headache index at baseline: 10.67
Martucci, 1985[144] Sample 20 Analyzed 20 % women 70	Ad hoc committee classification system Years of migraine: All participants had a clinical history longer than 5 years	Not reported Mean age 32.5 years	Not reported
Denaro, 1985[145] Sample 20 Analyzed 20 % women 70	Ad hoc committee classification system Years of migraine All participants had a clinical history longer than 5 years	Not reported Mean age 32.5 years	Not reported
Boisen, 1978[146] Sample 71 Analyzed 49 % women Not reported	Migraine was defined as paroxysmal headache associated with discomfort, possibly with inability to work, and one or more of the following symptoms: nausea, vomiting, visual disturbances and paresthesia Years of migraine: Not reported	16 to 60 years Not reported	7/49 had 4 migraine days monthly, 20/49 had 4-8 days with migraine, 21/49 had more than 8 days with migraine in past two months
Wilkinson, 1970[147] Sample 27 Analyzed 24 % women 89	Not reported Years of migraine: Not reported	Over 16 years of age Average age of men: 38, of women: 37.5	Not reported
Adam, 1978[148] Sample 96 Analyzed 70 % women 84.3	Not reported Years of migraine: Not reported	Not reported Mean age group one (clonidine to placebo) 40 years; mean age group two (placebo to clonidine) 35 years	Less than 3 headaches per 3 months 24/70 (34%), more than 3 headaches per 3 months 46/70 (66%)

Appendix Table D58. Randomized controlled clinical trials that examined clonidine for migraine prevention in adults (continued)

Reference Sample Analyzed % Women	Definition of Migraine Years of Migraine	Eligible Age of Subjects	Baseline Migraine Status
Bredfeldt, 1989[149] Sample 43 Analyzed 30 % women 80	Ad hoc committee on the classification of headache Years of migraine: Not reported	18 years or more Range 20-57 years	Not reported
Kallanranta, 1977[150] Sample 50 Analyzed 50 % women 72	Not reported Years of migraine: Not reported	Not reported mean age 31.6 years	24/50 (48%) with classic migraine, 26 (52%) with common migraine, 6/50 (12%) with dietary migraine, mean frequency of attacks was 3.94 (sd 2.19)
Kallanranta, 1977[150] Sample 50 Analyzed 50 % women 64	Not reported Years of migraine Not reported	Not reported Mean age 36.3 years	14/50 (28%) with classic migraine, 36/50 (72%) with common migraine, 3/50 (6%) with dietary migraine, mean frequency of attacks was 4 (sd 2.20)
Das, 1979[151] Sample 20 Analyzed 20 % women 70	Ad hoc committee on classification of headache Years of migraine: Not reported	Not reported 20-48 years	Not reported

Appendix Table D59. Sponsorship and conflict of interest in randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference	Sponsorship	Ethical Approval of Study	Consent of Participants	Conflict of Interest
Ryan, 1975[140]	Not reported	Not reported	Not reported	Not reported
Ryan, 1975[141]	Not reported	Not reported	Not reported	Not reported
Shafar, 1972[142]	Not reported	Not reported	Yes	Not reported
Stensrud, 1976[143]	Not reported	Not reported	Not reported	Not reported
Martucci, 1985[144]	Not reported	Not reported	Yes	Not reported
Denaro, 1985[145]	Not reported	Not reported	Yes	Not reported
Boisen, 1978[146]	Not reported	Not reported	Yes	Not reported
Wilkinson, 1970[147]	Not reported	Not reported	Yes	Not reported
Adam, 1978[148]	Industry (Boehringer Ingelheim Limited)	Not reported	Yes	Not reported
Bredfeldt, 1989[149]	Industry (Boehringer Ingelheim Pharmaceuticals)	Not reported	Yes	Not reported
Kallanranta, 1977[150]	Not reported	Not reported	Not reported	Not reported
Kallanranta, 1977[150]	Not reported	Not reported	Not reported	Not reported
Das, 1979[151]	Industry (Unichem Labs supplied medication)	Not reported	Not reported	Not reported

Appendix Table D60. Risk of bias in randomized controlled clinical trials that examined clonidine for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Ryan, 1975[140]	Double blind	Unclear	Unclear	Unclear	No	Low
Ryan, 1975[141]	Double blind	Unclear	Unclear	Unclear	No	Low
Shafar, 1972[142]	Double blind	No	Unclear	Unclear	No	Medium
Stensrud, 1976[143]	Double blind	No	Unclear	Unclear	No	Medium
Martucci, 1985[144]	Double blind	Unclear	Unclear	Unclear	No	Low
Denaro, 1985[145]	Double blind	Unclear	Unclear	Unclear	No	Low
Boisen, 1978[146]	Double blind	No	Unclear	Unclear	No	Medium
Wilkinson, 1970[147]	Double blind	No	Unclear	Unclear	Unclear, different dosages of clonidine not reported separately	Medium
Adam, 1978[148]	Double blind	No	Unclear	Yes	No	Medium
Bredfeldt, 1989[149]	Double blind	No	Unclear	Unclear	No	High
Kallanranta, 1977[150]	Not reported	Unclear	Unclear	Unclear	No	Unclear
Kallanranta, 1977[150]	Not reported	Unclear	Unclear	Unclear	No	Unclear
Das, 1979[151]	Double blind	Unclear	Unclear	Unclear	No	Low

Appendix Table D61. Randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference Sample Analyzed % Women	Definition of Migraine % Without Aura	Baseline Severity	Eligible Age Age of Subjects	Duration of Migraine Prior Treatment History
Martucci, 1983[152] Sample 90 Analyzed 79 % women 60	Common migraine (Ad Hoc Committee on Classification of Headache) 100 (assumed)	NR	Adults & Middle aged Mean: 36.6	NR NR
Herrmann, 1977[153] Sample 153 Analyzed unclear % women 73.2	NR 32.5 (assumed)	NR (Median frequency lies around 7-10 attacks per month)	NR NR (median lies around 20-40)	<1y: 6.8%, 1-5y: 35.8%, 5-10y: 15.9%, 10y: 37% NR
Whewell, 1966[154] Sample 74 Analyzed 50 % women 80	Migraine defined as a periodic throbbing headache, unilateral initially, with at least three of the following features: a) sensory prodromata, b) photophobia, c) nausea or vomiting, d) family history of migraine, and e) fluid retention before or diuresis during attack. NR	≥1 for 4 wks (from exclusion criterion)	Adolescent, Adults & Middle aged Mean: 42	20 NR
Pradalier, 2004[155] Sample 384 Analyzed 363 % women 80.7	Migraine (with or without aura) was based on criteria defined by the International Headache Society 36.9	Mean migraine attacks: 3.3	Adults & Middle aged Mean: 39.1	15.8 NR
Neuman, 1986[156] Sample 40 Analyzed 40 % women 45	Migraine NR	Mean migraine attacks: 3.3	Adults, Middle aged, & Aged Mean: 47	NR NR
Buscaino, 1991[157] Sample 90 Analyzed 90 % women 70	Migraine (Ad Hoc Committee) 100	NR (median lies around 5 to 6 attacks per month")	Adults & Middle aged Mean: 36.8	16 Flunarizine, ergot derivatives, and anti-depressants
Buscaino, 1991[157] Sample 18 Analyzed 13 % women 83.3	Common (n=16), Classic (n=1), Cluster (n=1) 88.9	NR	Adults & Middle aged Mean: 33.2	NR NR
Somerville, 1976[158] Sample 150 Analyzed 132 % women NR	Migraine defined as recurrent paroxysmal headache lasting a minimum of one hour and associated with at least one of the following symptoms: nausea, vomiting, photophobia, visual, motor or sensory symptoms or dysphasia NR	NR (Median frequency lies around 3-4 attacks per month)	NR NR	NR NR

Appendix Table D61. Randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults (continued)

Reference Sample Analyzed % Women	Definition of Migraine % Without Aura	Baseline Severity	Eligible Age Age of Subjects	Duration of Migraine Prior Treatment History
Bonuso, 1983[159] Sample 41 Analyzed unclear % women 68.3	Mixed headache diagnosed in accordance with the definitions of the "ad hoc Committee" 100 (assumed)	NR	Adults & Middle aged NR	NR NR

NR = Not reported

Appendix Table D62. Funding and conflict of interest in randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Martucci, 1983[152]	NR	NR	NR	NR	NR
Herrmann, 1977[153]	NR	NR	Yes	NR	NR
Whewell, 1966[154]	NR	NR	NR	NR	NR
Pradalier, 2004[155]	Industry	Yes	Yes	No	NA
Neuman, 1986[156]	NR	NR	NR	NR	NR
Buscaino, 1991[157]	NR	NR	Yes	NR	NR
Buscaino, 1991[157]	NR	NR	Yes (unclear if it is fully informed, but patients agreed to participate in the study)	NR	NR
Somerville, 1976[158]	NR	NR	NR	NR	NR
Bonuso, 1983[159]	NR	NR	NR	NR	NR

NR = not reported

Appendix Table D63. Risk of bias in randomized controlled clinical trials that examined ergot alkaloids for migraine prevention in adults

Reference	Masking of Treatment Status	ITT Planned	Allocation Concealment	Adequacy of Randomization	Adequacy of Randomization (Migraine Characteristics)	Selective Outcome Reporting	Risk of Bias
Martucci, 1983[152]	DB	No	Unclear	NR	NR	No	Medium
Herrmann, 1977[153]	DB	No	Unclear	Yes	F, S & D	Unclear	Medium
Whewell, 1966[154]	DB	No	Unclear	NR	NR	Unclear	Medium
Pradalier, 2004[155]	DB	Yes	Unclear	Yes	F & D	No	Low
Neuman, 1986[156]	DB	No	Unclear	Yes	F	Unclear	Medium
Buscaino, 1991[157]	DB	No	Unclear	Yes	F, S & D	Unclear	Medium
Buscaino, 1991[157]	DB	No	Unclear	NR	F	Unclear	Medium
Somerville, 1976[158]	DB	No	Unclear	NR	F	Unclear	Medium
Bonuso, 1983[159]	NR	No	Unclear	NR	S & D	Unclear	Medium

ITT = Intention to treat
F= frequency
S = severity
D = duration
DB = double blind
NR = not reported

Appendix Table D64. Randomized controlled clinical trials that examined comparative effectiveness of onabotulinumtoxin A for migraine prevention in adults

Reference	Country	Objective	Sample [Number Analyzed] % Women	Age	Definition of Migraine	Presence of Aura % Without Aura	Duration of Migraine, Years	Baseline Severity	Comorbidity
Millan-Guerrero, 2009[160]	Mexico	Histamine vs. botulinum toxin type A (BoNTA)	100 [100] 92% women	Mean: 33	International Headache Society	Included % without aura 81	15	Mean migraine frequency (days): 4.12	NR
Mathew, 2009[161]	USA	Onabotulinumtoxin A (BOTOX, Allergan, Inc) vs. topiramate (TOPAMAX, Ortho-McNeil)	60 [33] 90% women	Mean: 36.8	Migraine headache with or without aura occurring on >14 days/month for >3 months in the absence of medication overuse	Included % without aura NR	NR	Headache days: 15.6	NR
Magalhaes, 2010[162]	Brazil	Botulinum toxin type A vs. amitriptyline	72 [unclear] 97.2% women	Mean: 34.1	Chronic daily migraines, according to the International Classification of Headache Disorders-II	NR % without aura NR	NR	NR (Number of pain days at baseline: 24)	NR
Cady, 2011[163]	USA	Onabotulinumtoxin A vs. topiramate (CM)	59 [44] 91.5% women	Mean: 39.6	Chronic migraine (CM) fulfilling criteria of the Second Edition of the ICHD	NR % without aura NR	16 (median)	NR (Headache days/month: 21.1)	Every subject reported at least one problem with a body system (58/59, neurological; 39/59. psychological). A physical/neurological abnormality was found in 13.6% (8/59)
Blumenfeld, 2008[164]	USA	Botulinum toxin type A (BoNTA; BOTOX®: Allergan, Inc.) vs. divalproex sodium (DVPX; DEPAKOTE®: Abbott Laboratories)	59 [59] 84.7% women	Mean: 42.4	Episodic migraine (defined for this study as ≥3 migrainous headaches but <15 days	NR % without aura NR	NR	Number of headache days per month: 11.7	NR

Appendix Table D64. Randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults (continued)

Reference	Country	Objective	Sample [Number Analyzed] % Women	Age	Definition of Migraine	Presence of Aura % Without Aura	Duration of Migraine, Years	Baseline Severity	Comorbidity
					/month) or chronic migraine (defined for this study as migrainous headaches on 15 days/month)				

NR = not reported

Appendix Table D65. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults

Reference	Finance	Ethical Approval	Consent	Conflict of Interest	Conflict of Interest Disclosure
Millan-Guerrero, 2009[160]	Not reported	Yes	Yes	Not reported	Not applicable
Mathew, 2009[161]	Industry	Yes	Yes	Yes	Dr. Matthew is on the scientific advisory board of Merck, Allergan, and Ortho-McNeil. Hi is also on the speaker's bureau for Merck, GSK, Endo Pharmaceuticals, and Allergan.
Magalhaes, 2010[162]	Government	Yes	Yes	Not reported	Not applicable
Cady, 2011[163]	Not reported	Yes	Yes	Yes	Dr. Roger Cady: Consultant for GlaxoSmithKline, Merck, Ortho-McNeil. Research grants from Allergan, Endo Pharmaceuticals, GlaxoSmithKline, Merck, and Wyeth. Dr. John Porter: Consulting Speakers panel with Novartis, Forest, Biogen, UCB Pharma, Pfizer, TEVA. Dr. Andrew Blumenfeld: Consultant, speaker's bureau, and research grants from Allergan. Dr. Curtis Schreiber and Dr. Kathleen Farmer: None to disclose.
Blumenfeld, 2008[164]	Industry	Yes	Yes	Yes	Dr. Blumenfeld has received honoraria for speaking activities and a research grant from Allergan, Inc. Dr. Schim has received research grants from Allergan, Inc., has been a consultant for Allergan, Inc., and serves on the speaker's bureau for Allergan. He has received research grants from Boehringer, Pfizer, GlaxoSmithKline, Merck, Astra-Zeneca, and Ortho-McNeil. He serves on the speaker's bureau for Boehringer, Pfizer, GlaxoSmithKline, Merck, and Ortho-McNeil. Dr. Chippendale has received personal compensation from Allergan, Inc., and Photothera for consulting services. He received personal compensation from Boehringer Ingelheim, Pfizer, and Teva for speaking.

Appendix Table D66. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of botulinum toxin for migraine prevention in adults

Reference	Masking of Treatment	Planned Intention to Treat Analysis	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias	Other Concerns
Millan-Guerrero, 2009[160]	Double blind	No	Unclear	Yes	Unclear	Low	Poor reporting quality
Mathew, 2009[161]	Double blind	No	Unclear	No	Unclear	Medium	
Magalhaes, 2010[162]	Open label	No	Unclear	Unclear (age seems to differ by groups; no tests conducted)	Unclear	High	
Cady, 2011[163]	Double blind	No	Unclear	Unclear (unclear in demographic characters, but adequate in migraine characteristics)	Unclear	Medium	
Blumenfeld, 2008[164]	Double blind	Yes	Unclear	No	Unclear	Medium	Baseline Headache severity differs by groups

Appendix Table D67. Comparative effectiveness of onabotulinumtoxin A vs. topiramate in migraine prevention (results from individual randomized controlled clinical trials)

Outcome	Reference Risk of Bias	Active vs. Control Drug	Events/ Randomized with Active Drug	Events/ Randomized with Control Drug	Relative Risk 95% CI)	Absolute Risk Difference (95% CI)
At least a 50% reduction in headache days per month	Cady, 2011[163] Medium	Topiramate vs. Onabotulinumtoxin A	12/30	9/29	1.3 (0.6 to 2.6)	0.09 (-0.15 to 0.33)
≥ 50% reduction in HA/migraine days	Mathew, 2009[161] High	Topiramate plus placebo injection vs. Onabotulinumtoxin A (Botox) + Oral placebo	9/30	9/30	1.0 (0.5 to 2.2)	0.00 (-0.23 to 0.23)
Migraine Disability Assessment (MIDAS) total score >21 (severe disability)	Mathew, 2009[161] High	Topiramate plus placebo injection vs. Onabotulinumtoxin A (Botox) + Oral placebo	7/30	6/30	1.2 (0.4 to 3.1)	0.03 (-0.17 to 0.24)
≥ 50% improvement in the Migraine Disability Assessment (MIDAS) total score	Mathew, 2009[161] High	Topiramate plus placebo injection vs. Onabotulinumtoxin A (Botox) + Oral placebo	12/30	11/30	1.1 (0.6 to 2.1)	0.03 (-0.21 to 0.28)
Physician global assessment: marked improvement	Cady, 2011[163] Medium	Topiramate vs. Onabotulinumtoxin A	10/30	10/29	1.0 (0.5 to 2.0)	-0.01 (-0.25 to 0.23)
Physician global assessment: moderate improvement	Cady, 2011[163] Medium	Topiramate vs. Onabotulinumtoxin A	6/30	4/29	1.5 (0.5 to 4.6)	0.06 (-0.13 to 0.25)
Physician global assessment: slight improvement	Cady, 2011[163] Medium	Topiramate vs. Onabotulinumtoxin A	1/30	5/29	0.2 (0.0 to 1.6)	-0.14 (-0.29 to 0.01)
Physician Global Assessment - response to treatment: Marked improvement (defined as at least 75% improvement)	**Mathew, 2009[161] Medium**	**Topiramate plus placebo injection vs. Onabotulinumtoxin A (Botox) + Oral placebo**	**18/30**	**8/30**	**2.3 (1.2 to 4.4)**	**0.33 (0.10 to 0.57)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D68. Comparative effectiveness of onabotulinumtoxin A vs. divalproex sodium in migraine prevention (results from a single medium risk of bias randomized controlled clinical trial)[165]

Outcome	Active vs. Control Drug	Events/ Randomized with Active Drug	Events/ Randomized with Control Drug	Relative Risk 95% CI)	Absolute Risk Difference (95% CI)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	2/7	0/7	5.0 (0.3 to 88.5)	0.29 (-0.08 to 0.65)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	2/7	2.0 (0.5 to 7.6)	0.29 (-0.21 to 0.78)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	4/7	1.0 (0.4 to 2.5)	0.00 (-0.52 to 0.52)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	4/7	3/7	1.3 (0.5 to 3.9)	0.14 (-0.38 to 0.66)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	5/22	4/23	1.3 (0.4 to 4.2)	0.05 (-0.18 to 0.29)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	10/22	17/23	0.6 (0.4 to 1.0)	**-0.28 (-0.56 to -0.01)**
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	12/22	12/23	1.0 (0.6 to 1.8)	0.02 (-0.27 to 0.32)
≥50% reduction in attack frequency per month	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	12/22	16/23	0.8 (0.5 to 1.3)	-0.15 (-0.43 to 0.13)
≥75% reduction in Migraine Disability Assessment Scores (MIDAS)	Divalproex sodium (plus placebo BoNTA) vs. Botulinum toxin type A (plus placebo-tablets)	5/29	16/30	0.3 (0.1 to 0.8)	-0.36 (-0.59 to -0.14)

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D69. Comparative effectiveness of onabotulinumtoxin A vs. amitriptyline in migraine prevention (results from a single high risk of bias randomized controlled clinical trial)[162]

Outcome	Active vs. Control Drug	Events/ Randomized with Active Drug	Events/ Randomized with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Physician assessment: improvement	Amitriptyline vs. Botulinum toxin type A	32/37	31/35	1.0 (0.8 to 1.2)	-0.02 (-0.17 to 0.13)
Patient self assessment: improvement	Amitriptyline vs. Botulinum toxin type A	33/37	29/35	1.1 (0.9 to 1.3)	0.06 (-0.10 to 0.22)
Improvement a) any single criterion met among objective criteria: a) a reduction by at least 50% in the number of pain episodes, b) a reduction in the intensity of pain of at least 3 point, and c) a reduction by at least 50% in the number of pain drug doses used for migraine	Amitriptyline vs. Botulinum toxin type A	35/37	31/35	1.1 (0.9 to 1.2)	0.06 (-0.07 to 0.19)
A reduction by at least 50% in the number of pain drug doses used for migraines	Amitriptyline vs. Botulinum toxin type A	26/37	27/35	0.9 (0.7 to 1.2)	-0.07 (-0.27 to 0.13)
A reduction by at least 50% in the number of days of pain	Amitriptyline vs. Botulinum toxin type A	27/37	24/35	1.1 (0.8 to 1.4)	0.04 (-0.17 to 0.25)

CI = confidence interval

Appendix Table D70. Randomized controlled clinical trials of comparative effectiveness of topiramate for migraine prevention in adults (all trials did not report prior migraine preventive treatments)

Reference	Country	Total Sample [Number Analyzed] % Females	Age	Definition of Migraine	Presence of Aura	Duration of Migraine	Migraine Frequency/ Month	Baseline Comorbidity
Bartolini, 2005[166]	Italy	49 [44] 70.5% females	Mean 41.8 years	International Headache Society Classification of Head and Facial Pain	Patients having migraine without aura were included in the study	5.45 years	26.6	Not reported
Shaygannejad, 2006[167]	Iran	64 [64] 56.3% females	Mean 34.1 years	International Headache Society criteria	Not reported	11.2 years	5.4	Not reported
Gupta, 2007[44]	India	60 [Variable] 78.3% females	Mean 29.41 years	International Headache Society criteria	31.67% had aura	5.08 years	6.98	30% of patients had premigrainous depression
de Tommaso, 2007[168]	Italy	45 [39] 86.0% females	Mean 37.86 years	Headache Classification Committee, 2004	None of the patients had aura	Not reported	Not reported	Not reported
Millan-Guerrero, 2008[169]	Not reported	90 [90] 86.0% females	Mean 32 years	International Headache Society criteria	With aura (n): Histamine:3, Topiramate: 5, Without aura (n); Histamine: 42, Topiramate: 40	14.8 years	4.1	Not reported
Keskinbora, 2008[170]	Turkey	75 [63] 66.7% females	Mean 37.5 years	International Headache Society criteria	Not reported	Not reported	6.1	Beck Depression Inventory BDI-II score: Topiramate: 17.95±5.64, Amitriptyline: 17.05±8.90, Combined: 16.95±6.05
Ashtan, 2008[171]	Iran	62 [60] 81.7% females	Mean 30.5 years	International Headache Society	Not reported	At least 1 year	5.9	Not reported

Appendix Table D70. Randomized controlled clinical trials of comparative effectiveness of topiramate for migraine prevention in adults (all trials did not report prior migraine preventive treatments) (continued)

Reference	Country	Total Sample [Number Analyzed] % Females	Age	Definition of Migraine	Presence of Aura	Duration of Migraine	Migraine Frequency/ Month	Baseline Comorbidity
Dodick, 2009[172]	USA	347 [Variable] 84.9% females	Mean 38.8 years	International Headache Society 1.1 or 1.2	Not reported	Age at migraine onset: 20.25 years	6.15	Not reported
Mohammadianinejad, 2011[173]	Iran	80 [75] 78.8% females	Mean 34.2 years	International Headache Society criteria	Not reported	9.9 years	7.4	Not reported

Appendix Table D71. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of topiramate for migraine prevention in adults

Reference	How Project was Funded	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests - Relationship
Bartolini, 2005[166]	Not reported	Yes	Yes	Not reported	Not applicable
Shaygannejad, 2006[167]	Not reported	Yes	Yes	Not reported	Not applicable
Gupta, 2007[44]	Not reported	Yes	Yes	None	Not applicable
de Tommaso, 2007[168]	Not reported	Yes	Yes	Not reported	Not applicable
Millan-Guerrero, 2008[169]	Not reported	Yes	Yes	Not reported	Not applicable
Keskinbora, 2008[170]	Not reported	Yes	Yes	Not reported	Not applicable
Ashtan, 2008[171]	Not reported	Yes	Yes	Not reported	Not applicable
Dodick, 2009[172]	Industry	Yes	Yes	Not reported	Not reported, however, Jim Xiang, Marcia Rupnow, and David Biondi are employees of Ortho-McNeil Janssen Scientific Affairs, LLC, Titusville, New Jersey
Mohammadianinejad, 2011[173]	Other	Yes	Yes	None	Not applicable

Appendix Table D72. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of topiramate for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Bartolini, 2005[166]	Open-label	Not reported	Unclear	No (Females were more in the valproate group and males in the topiramate group)	Unclear	High
Shaygannejad, 2006[167]	Double-blind	Yes	Unclear	No (sodium valproate group had slightly more severe headache and lower duration of migraine than topiramate group)	Unclear	Medium
Gupta, 2007[44]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
de Tommaso, 2007[168]	Double-blind	No	Unclear	Not reported	Unclear	Medium
Milan-Guerrero, 2008[169]	Double-blind	No	Unclear	Yes	Unclear	Low
Keskinbora, 2008[170]	Double-blind	No	Unclear	Yes	Unclear	Medium
Ashtari, 2008[171]	Double-blind	No	Unclear	Yes	Unclear	Medium
Dodick, 2009[172]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mohammadianinejad, 2011[173]	Double-blind	No	Clearly adequate	Yes	Unclear	Medium

Appendix Table D73. Comparative effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials)

Definition of the Outcome	Active Drug Daily Dose	Control Drug Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Decrease in headache days by more than 50%	**Topiramate 100mg**	**Amitriptyline 100mg**	**Dodick, 2009[172] Low**	**97/178 [54.4]**	**74/169 [43.9]**	**1.2 (1.0 to 1.5)**	**0.11 (0.00 to 0.21)**
Decrease in migraine by more than 50%	Topiramate 100mg	Amitriptyline 100mg	Dodick, 2009[172] Low	99/178 [55.6]	78/169 [45.9]	1.2 (1.0 to 1.5)	0.09 (-0.01 to 0.20)
Decrease in headache frequency by more than 50%	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	38/60 [63.0]	28/60 [46.0]	1.4 (1.0 to 1.9)	0.17 (-0.01 to 0.34)
Headache intensity (≥50% reduction in mean migraine intensity)	**Topiramate 25mg BD**	**Lamotrigine 25mg BD**	**Gupta, 2007[44] Low**	**30/60 [50.0]**	**13/60 [21.0]**	**2.3 (1.3 to 4.0)**	**0.28 (0.12 to 0.45)**
Migraine frequency of less than 50% of the basal frequency	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[168] Medium	8/13 [61.5]	8/15 [53.3]	1.2 (0.6 to 2.2)	0.08 (-0.28 to 0.45)
Reduction of at least 50% in days with headache	Topiramate 75mg/day (25mg in the morning and 50mg in the evening)	Valproate(Slow-release) 750mg/day (250mg in the morning and 500mg in the evening)	Bartolini, 2005[166] High	20/22 [90.9]	21/22 [95.5]	1.0 (0.8 to 1.1)	-0.05 (-0.19 to 0.10)
Decrease in headache frequency by more than 50%	Topiramate 25mg/day, gradually titrated up to 100mg/day	Zonisamide 50mg/day, gradually titrated up to 200mg/day	Mohammadianinejad, 2011[173] Medium	16/40 [40.0]	15/40 [37.5]	1.1 (0.6 to 1.9)	0.03 (-0.19 to 0.24)
Presence of concomitant symptoms	Topiramate 200mg	Amitriptyline 150mg of 150mg/day)	Keskinbora, 2008[170] Medium	3/24 [12.5]	8/28 [28.6]	0.4 (0.1 to 1.5)	-0.16 (-0.37 to 0.05)
Presence of concomitant symptoms	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline	Amitriptyline 150mg	Keskinbora, 2008[170] Medium	5/23 [21.7]	8/28 [28.6]	0.8 (0.3 to 2.0)	-0.07 (-0.31 to 0.17)

Appendix Table 73. Comparative effectiveness of topiramate for migraine prevention in adults (individual randomized controlled clinical trials (continued)

Definition of the Outcome	Active Drug Daily Dose	Control Drug Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline						
Presence of concomitant symptoms	Topiramate 200mg	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Keskinbora, 2008[170] Medium	3/24 [12.5]	5/23 [21.7]	0.6 (0.2 to 2.1)	-0.09 (-0.31 to 0.12)

Bold = differences are statistically significant when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D74. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
Ashtari, 2008[171] Sample Not reported 81.7% women	To assess the efficacy and safety of low-dose topiramate in migraine prophylaxis vs. propranolol	International Headache Society	Not reported	Mean: 30.8	Mean monthly headache frequency: 5.95
Behan, 1980[174] Sample 56 66.1% women	To compare propranolol with methysergide in a large group of patients with chronic, incapacitating migraine	Chronic, incapacitating migraine	0.5 to 33	Not reported	Not reported; inclusion criterion: at least two attacks of severe migraine per month
Rafieian-Kopaei, 2005[64] Sample 105 % women Not reported	To compare the prophylactic activity of propranolol and amitriptyline on frequency, duration and severity of migraine attacks	Migraine (International Headache Society)	>1 (from inclusion criteria)	Not reported	Mean attack frequency: 4.02 (per month)
Kangasniemi, 1983[77] Sample 29 86.2% women	1) To compare the relative efficacy of propranolol and femoxetine in migraine prophylaxis, and 2) to assess the usefulness of steady state VEP (visual evoked potential) recording in the evaluation of drug effects on migraine.	Common and classic migraine	17	37	Mean frequency of migraine attacks: 7.18
Domingues, 2009[75] Sample 76 % women Not reported	To evaluate the short term efficacy and safety of the combination of low doses of propranolol and nortriptyline compared to these drugs alone	International Headache Society	Not reported	Not reported	Not reported
Carroll, 1990[175] Sample 55 69% women	To compare the efficacy and tolerability of two long-acting formulations of propranolol	Classical or common migraine (Ad hoc committee classification of headache)	Median: 14	Mean: 39	Mean frequency of migraine (month): 6.1
Kaniecki, 1997[68] Sample 37 81% women	To compare the efficacy of divalproex sodium (Depakote) with that of	Migraine without aura as defined by the International Headache	Not reported	Not reported	Mean attacks (month): 4.38

Appendix Table 74. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
	propranolol hydrochloride (and placebo) for the prophylaxis of migraine without aura	Society			
Ziegler, 1987[76] Sample 54 73% women	To compare efficacy of propranolol and amitriptyline in the prophylaxis of migraine headache	Patients were admitted to the study when two senior neurologists agreed on the diagnosis of migraine based on the frequent occurrence of the following factors: 1) unilateral nature of the headache; 2) nausea and/or vomiting, 3) premonitory visual phenomena, and 4) headache with no consistent association with transient stress or anxiety	Not reported	Mean: 38	More than half of the headache episodes were classified as either "severe" (defined as "able to carry on some activities with discomfort but not with normal efficiency") or "disabling" (defined as "cannot carry on any normal activity, must go to bed")
Kaushik, 2005[176] Sample 192 69% women	To evaluate utility of biofeedback assisted diaphragmatic breathing and systematic relaxation in migraine and to compare their efficacy with propranolol in long term prophylaxis of migraine	International Headache Society	Not reported	Not applicable	Frequency of migraine episodes (per month): 4-5 (propranolol vs. biofeedback, 71.9% and 76%, respectively)
Kangasniemi, 1984[70] Sample 36 89% women	To compare the well-established migraine prophylactic effect of the non-selective beta-blocker propranolol with that of the beta1-selective beta-blocker metoprolol	World Federation of Neurology Research Group on Migraine and Headache, 1969	15.6	Mean: 33.8	Number of migraine attacks per 4 weeks: 5.3
Tfelt-Hansen, 1984[60] Sample 96 74% women	To compare the beta-adrenergic blocker timolol to an established drug,	Between 2 and 6 common migraine attacks per month as defined by the	20.9	Mean: 39.5	Number of migraine attacks per 4 weeks: 5.7

Appendix Table 74. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
	propranolol, and to placebo for prophylactic effect in common migraine	ad hoc committee and by Olsen			
Olerud, 1986[73] Sample 28 % women 79	To compare the prophylactic efficacy of nadolol with that of propranolol in patients with classic or common migraine	Classic and/or common migraine headaches as set forth by the Ad Hoc Committee on the Classification of Headache	Range: 2-45	Not reported (range: 17-61)	Median number of migraine attack per month during single blind placebo period: 5.6 (Nadolol), 3.6 (Propranolol)
Mathew, 1981[105] Sample 715 94.5% women	To determine propranolol long-term effectiveness and tolerance, and to the patient's migraine status after termination of therapy	Not reported	Not reported	Mean: 38	Not reported
Albers, 1989[74] Sample 40 89.5% women	To compare the effectiveness of nifedipine to that of propranolol in the initial prophylaxis of migraine headache	Ad Hoc Committee on the Classification of Headache	Not reported	Mean: 35.2	5.2
Andersson, 1981[177] Sample 49 69.4% women	To compare the prophylactic effect of femoxetine with the effect of propranolol (Frekven) in a double-blind crossover study	Migraine was defined as paroxysmal headache associated with discomfort, possibly with inability to work, and one or more of the following symptoms: nausea, vomiting, visual disturbances and paresthesia.	Not reported	Mean: 38	Migraine attacks per 4 weeks: 5.7
Kass, 1980[69] Sample 23 69.6% women	To compare the prophylactic effect on migraine of propranolol and clonidine	World Federation of Neurology, 1969	Not reported	Mean: 39.7	Not reported
Havanka-Kanniainen, 1988[178] Sample Not reported 81% women	To compare the efficacy and side-effects of LA propranolol 80 mg once a day with that of LA propranolol 160 mg once daily in the prophylactic	Ad Hoc Committee on the Classification of Headache	17.5	Mean: 37.7	Migraine attack: 5.1

Appendix Table 74. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
	treatment of classic and common migraine				
Olerud, 1986[73] Sample 42 % women Not reported	To evaluate the effectiveness of a Beta-blocker (propranolol) alone, a calcium antagonist (cinnarizine) alone, and both in combination	Not reported	Not reported	Not reported	Not reported
Solomon, 1986[179] Sample Not reported % women Not reported	To compare the prophylactic antimigraine effect of the calcium entry blocker verapamil with beta-blocker propranolol	Not reported	Not reported	Not reported	Not reported
Ryan, 1984[180] Sample 48 73% women	To compare the relative efficacy and safety of propranolol and nadolol in the prophylactic phase of the treatment of migraine	Common or classical migraine (no definition provided)	Not reported	Not reported	Headache frequency/4 weeks: 6.3
Gerber, 1991[71] Sample 58 81% women	To ascertain, on the basis of single case statistics and time-series analysis, responder and non-responder rates for metoprolol, propranolol and nifedipine in migraine prophylaxis. In addition, an attempt was made to identify the dose relationship for the various drugs on headache parameters.	Common or classical migraine (no definition provided)	21	Mean: 42.4	Headache frequency/4 weeks: 3.55
Sudilovsky, 1987[72] Sample 140 76% women	To compare the effects of nadolol with those of propranolol in the prophylactic treatment of migraine	Classic or common migraine as defined by Ad Hoc Committee on Classification of Headache	20.7	Mean: 39.3	Headache frequency/4 weeks (during last year): 5.29
Stensrud, 1980[62] Sample 35	To compare the effectiveness of a selective	Ad Hoc Committee on Classification of	Not reported	Not reported	Not reported

Appendix Table 74. Randomized controlled clinical trials that examined comparative effectiveness of propranolol of migraine prevention in adults (continued)

Reference Total Sample Size as Randomized % Women	Aim	Definition of Migraine	Duration of Migraine, Years	Age of Subjects	Baseline Severity
68.6% women	and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Headache (1962)			
Olsson, 1984[181] Sample 56 73.2% women	To investigate the prophylactic effect of metoprolol under double-blind controlled conditions and to compare the effect with that of propranolol in dosages that could be regarded as starting dosage	Classical or common migraine (defined by the World Federation of Neurology Research Group on Migraine and Headache, 1969/18/)	20.7	Mean: 39.6	Migraine attack (median) / 4 weeks (during placebo run in): 5.4
Ahuja, 1985[56] Sample 26 46.2% women	To compare the effectiveness of a selective and a non-selective beta1-receptor antagonist i.e. atenolol (Tenormin) and propranolol (Inderal), in the prophylaxis of migraine	Ad Hoc Committee on Classification of Headache (1962)	Not reported	Not reported	Not reported
Sargent, 1985[55] Sample 149 79% women	To evaluate the prophylactic effect and tolerance of naproxen sodium compared to propranolol hydrochloride and placebo in migraine	Common or classical migraine, or a combination migraine and muscle contraction headache (no definition provided)	20	Mean: 30	Not reported
Standnes, 1982[61] Sample 25 80% women	To evaluate the prophylactic effect of timolol in migraine	Common migraine attacks (as defined by the Ad Hoc Committee)	Not reported	Mean: 41.4	Mean number of attacks (4 weeks): 6.65
Diener, 2004[43] Sample 575 79.8% women	To evaluate the efficacy and safety of two doses of topiramate and safety of two doses of topiramate vs. placebo for migraine prophylaxis, with propranolol (PROP) as an active control	International Headache Society	Not reported	Median: 41	Mean monthly migraine frequency: 5.1

Appendix Table D75. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Ashtari, 2008[171]	Not reported	Yes	Yes	Not reported	Not reported
Behan, 1980[174]	Other	Not reported	Not reported	Not reported	Not reported
Rafieian-Kopaei, 2005[64]	Other	Not reported	Yes	Not reported	All authors are from the University that sponsored the study
Kangasniemi, 1983[77]	Not reported	Not reported	Not reported	Not reported	Not reported
Domingues, 2009[75]	Not reported	Yes	Yes	Not reported	Not reported
Diener, 2002[182]	Industry	Yes	Yes	Not reported	Not reported
Carroll, 1990[175]	Not reported	Yes	Yes	Unclear	One of author is employed by industry (ICI pharmaceuticals), but unclear their relationship (no funding source reported.)
Kaniecki, 1997[68]	Industry	Not reported	Yes	Not reported	Not reported
Ziegler, 1987[76]	Grant	Not reported	Not reported	Not reported	Not reported
Kaushik, 2005[176]	Other	Yes	Yes	Not reported	Not reported
Kangasniemi, 1984[70]	Not reported	Not reported	Yes	Not reported	Not reported
Tfelt-Hansen, 1984[60]	Not reported	Not reported	Yes	Not reported	Not reported
Olerud, 1986[73]	Not reported	Not reported	Yes	Not reported	Not reported
Mathew, 1981[105]	Not reported	Not reported	Not reported	Not reported	Not reported
Albers, 1989[74]	Industry + Grant	Not reported	Yes	No	Not reported
Andersson, 1981[177]	Not reported	Not reported	Not reported	Not reported	Not reported
Kass, 1980[69]	Industry	Not reported	Not reported	Not reported	Not reported
Havanka-Kanniainen, 1988[178]	Industry	Yes	Not reported	Not reported	Not reported
Olerud, 1986[73]	Not reported	Not reported	Not reported	Not reported	Not reported
Solomon, 1986[179]	Not reported	Not reported	Not reported	Not reported	Not reported
Ryan, 1984[180]	Not reported	Not reported	Yes	Not reported	Not reported
Gerber, 1991[71]	Not reported	Not reported	Not reported	Not reported	Not reported
Sudilovsky, 1987[72]	Not reported	Yes	Yes	Not reported	Not reported
Stensrud, 1980[62]	Not reported	Not reported	Not reported	Not reported	Not reported
Olsson, 1984[181]	Not reported	Yes	Yes	Not reported	Not reported
Ahuja, 1985[56]	Industry (Inderal brand of propranolol and identical looking placebo tablets were supplied by Alkali and Chemical Corp. India Ltd.	Not reported	Not reported	Not reported	Not reported
Sargent, 1985[55]	Not reported	Not reported	Not reported	Not reported	Not reported
Standnes, 1982[61]	Industry	Not reported	Yes	Not reported	Not reported

Appendix Table D75. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults (continued)

Reference	Funding	Ethical Approval	Consent	Conflict of Interest	Disclosed Relationships
Diener, 2004[43]	Industry	Yes	Yes	Yes	Hans-Christoph Diener has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from 3M Medica, Allergan, Almirall Prodesfarma, AstraZeneca, Bayer Vital, Böhringer Ingelheim, Bristol-Myers Squibb, Eisai, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, La Roche, Lilly, Novartis, MSD, Parke-Davis, Pfizer, Pharmacia, Pierre Fabre, Schaper and Brümmer, and Weber & Weber. Peer Tfelt-Hansen has been a consultant/scientific advisor for, and/or has received honoraria for oral presentation from Almirall Prodesfarma, AstraZeneca, GlaxoSmithKline, Johnson & Johnson, MSD, Pfizer, and Quintiles. Carl Dahlöf has been a consultant/scientific advisor for, and has received honoraria for oral presentations from Allergan, Almirall Prodesfarma, AstraZeneca, Bristol-Myers Squibb, GlaxoSmithKline, Jansen-Cilag, Johnson & Johnson, Lilly, MSD, Novartis, Pfizer, Pharmacia, and Pierre Fabre. Miguel JA Láinez has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Almirall Prodesfarma, AstraZeneca, Böhringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen-Cilag, Johnson & Johnson, MSD, Novartis, Pfizer, Pierre Fabre, and Sanofi-Synthelabo. Giorgio Sandrini has received grant/research support from, has been a consultant/scientific advisor for, and/or has received honoraria for oral presentations from Allergan, AstraZeneca, Bayer, Bristol- Myers Squibb, GlaxoSmithKline, Grünenthal, Janssen-Cilag, Johnson & Johnson, Lilly, MSD, Pfizer, Pharmacia, and Solvay Pharma. Shuu-Jiun Wang has received grant/research support from and/or received honoraria for oral presentations from AstraZeneca, Glaxo- SmithKline, Johnson & Johnson, Lilly, MSD, and Pfizer. Walter Neto, Ujjwalla Vijapurkar, Aiden Doyle, and David Jacobs are employed by Johnson & Johnson Pharmaceutical Research and Development, LLC.

Appendix Table D76. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of propranolol for migraine prevention in adults

Reference	Masking Treatment Status	Planned Intention to Treat	Allocation Concealment	Baseline Similarity in Migraine	Selective Outcome Reporting	Risk of Bias
Ashtari, 2008[171]	Double blind	No	Unclear	F & S	Unclear	Medium
Behan, 1980[174]	Double blind	No	Unclear	D	Unclear	Medium
Rafieian-Kopaei, 2005[64]	Double blind	No	Unclear	F	Unclear	Medium
Kangasniemi, 1983[77]	Double blind	No	Unclear	Not reported	Unclear	Medium
Domingues, 2009[75]	Double blind	No	Unclear	Not reported	Unclear	Medium
Diener, 2002[182]	Double blind	Yes	Unclear	F	Unclear	Low
Carroll, 1990[175]	Double blind	No	Unclear	F & S	Unclear	Medium
Kaniecki, 1997[68]	Single blind	No	Unclear	Not reported	Unclear	High
Ziegler, 1987[76]	Double blind	No	Unclear	S	Unclear	Medium
Kaushik, 2005[176]	Single blind	Yes	Adequate	F & S	Unclear	Medium
Kangasniemi, 1984[70]	Double blind	No	Unclear	Not reported	Unclear	Medium
Tfelt-Hansen, 1984[60]	Double blind	No	Unclear	F, S & D	Unclear	Medium
Olerud, 1986[73]	Double blind	No	Unclear	F	Unclear	Medium
Mathew, 1981[105]	Open-label	No	Unclear	Not reported	Unclear	High
Albers, 1989[74]	Open-label	No	Unclear	F	Unclear	High
Andersson, 1981[177]	Double blind	No	Unclear	Not reported	Unclear	Medium
Kass, 1980[69]	Double blind	No	Unclear	Not reported	Unclear	Medium
Havanka-Kanniainen, 1988[178]	Double blind	No	Unclear	Not reported	Unclear	Medium
Olerud, 1986[73]	Double blind	No	Unclear	Not reported	Unclear	Low
Solomon, 1986[179]	Double blind	No	Unclear	Not reported	Unclear	Medium
Ryan, 1984[180]	Double blind	No	Unclear	Not reported	Unclear	Medium
Gerber, 1991[71]	Double blind	No	Unclear	F & D	Unclear	Medium
Sudilovsky, 1987[72]	Double blind	No	Unclear	F & D	Unclear	Medium
Stensrud, 1980[62]	Double blind	No	Unclear	Not reported	Unclear	Medium
Olsson, 1984[181]	Double blind	No	Unclear	Not reported	Unclear	Medium
Ahuja, 1985[56]	Double blind	No	Unclear	Not reported	Unclear	Low
Sargent, 1985[55]	Double blind	No	Unclear	Not reported	Unclear	Medium
Standnes, 1982[61]	Double blind	No	Unclear	Not reported	Unclear	Medium
Diener, 2004[43]	Double blind	Yes	Unclear	F	Unclear	Low

F = migraine frequency; S = migraine severity; D = migraine duration

Appendix Table D77. Randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference Aim	Total Sample [Number Analyzed] % Females in Sample	Definition of Migraine	Duration of Migraine	Presence of Aura	Migraine Frequency at Baseline/Month	Age of Subjects (Mean or Median)
Louis, 1985[183] To compare the effect of clonidine with that of the β1-selective β-adreno-receptor antagonist metoprolol in patients with classical and common migraine.	33 [31] 80.6	World Federation of Neurology Research Group on Migraine and Headache, 1969	18.7 years	Not reported	3 to 10 (inclusion criterion)	Mean 35.5 years
Langohr, 1985[184] To compare the efficacy of clomipramine, a serotonin-reuptake inhibitor, as anti-migraine drug, with that of metoprolol, a beta-blocking agent	63 [34] 66.7	Ad Hoc Committee on classification of headache	20.8 years	Since 13 patients had classical migraine it was assumed that these patients had migraine with aura	Not reported	Mean 44.4 years
Grotemeyer, 1990[185] To compare in a double-blind cross-over study with a well-demarcated run-in period the effectiveness of ASA with that of a well-established beta-blocker	28 [Not reported] 82.1	Ad hoc Committee	10 years	None of the patients had aura	4 to 8	Mean 31 years
Worz, 1991[186] To compare the efficacy and safety of bisoprolol (5-10mg once daily) in migraine prophylaxis with that of the beta1-selective blocker metoprolol (50-100mg twice daily), a well established migraine prophylactic drug	78 [Variable] 80.8	International Headache Society criteria	At least 2 years	55 had migraine without aura and 23 had migraine with aura	4	Not reported
Worz, 1992[187] To compare bisoprolol	125 [78] 77.6	International Headache Society	19.5 years	Migraine with aura: 27.2% and migraine	4.01	Mean 38.5 years

Appendix Table D77. Randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults (continued)

Reference Aim	Total Sample [Number Analyzed] % Females in Sample	Definition of Migraine	Duration of Migraine	Presence of Aura	Migraine Frequency at Baseline/Month	Age of Subjects (Mean or Median)
5mg once daily with metoprolol 50mg twice daily in migraine prophylaxis		criteria (Olesen, 1988)		without aura:72.8%		
Diener, 2001[188] To show equivalence of Aspirin with metoprolol with respect to efficacy, defined as a 50% reduction in the rate of migraine attacks.	270 [270] 81.1	International Headache Society criteria	13.8 years	50 Patients had migraine with aura	3.5	Mean 41.25 years
Schellenberg, 2008[189] To evaluate the efficacy of oral treatment with nebivolol and metoprolol in the prophylaxis of migraine attacks.	30 [30] 86.7	International Headache Society criteria -II: 1.1 and 1.2	17 years	Headache with aura/other symptoms: n (%): Metoprolol: 14 (100), Nebivolol: 15 (94)	3.4	Mean 39 years

Appendix Table D78. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Disclosed Relationships
Louis, 1985[183]	Not reported	Yes	Yes	Not reported	Not applicable
Langohr, 1985[184]	Industry	Not reported	Not reported	Not reported	Not applicable
Grotemeyer, 1990[185]	Not reported	Not reported	Not reported	Not reported	Not applicable
Worz, 1991[186]	Not reported	Not reported	Not reported	Not reported	Not applicable
Worz, 1992[187]	Not reported	Yes	Yes	Not reported	Not applicable
Diener, 2001[188]	Industry	Yes	Yes	Yes	G.Latta is from Bayer, Leverkusen, Germany
Schellenberg, 2008[189]	Industry	Yes	Yes	None	Not applicable

Appendix Table D79. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of beta-blockers for migraine prevention in adults

Reference	Masking of the Treatment Status	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Baseline Similarity	Selective Outcome Reporting	Risk of Bias
Louis, 1985[183]	Double-blind	No	Unclear	Not reported	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Medium
Langohr, 1985[184]	Double-blind	No	Unclear	Not reported	Not reported	Unclear	Medium
Grotemeyer, 1990[185]	Double-blind	No	Unclear	Not reported	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Medium
Worz, 1991[186]	Double-blind	No	Unclear	Not reported	Frequency: similar; Severity: not reported; Duration: not reported	Unclear	Medium
Worz, 1992[187]	Double-blind	No	Unclear	Not reported	Frequency: similar: Severity: not reported: Duration: not reported	Unclear	Medium
Diener, 2001[188]	Double-blind	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Unclear	Low
Schellenberg, 2008[189]	Double-blind	Yes	Unclear	No, there were no males in the metoprolol group	Frequency: similar; Severity: similar; Duration: similar	Unclear	Medium

Appendix Table D80. Strength of evidence of comparative effectiveness of beta-blockers for migraine prevention in adults

Definition of the Outcome	Reference	Active Drug	Control Drug	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Reduction of frequency of attacks by more than 50%	Worz, 1992[187]	Metoprolol	Bisoprolol	Medium	Yes	Not applicable	No	Low
Responder rate(at least 50% in number of attacks from baseline to endpoint)	Schellenberg, 2008[189]	Metoprolol	Nebivolol	Medium	Yes	Not applicable	No	Low
Reduction of attacks more than 50%	Grotemeyer, 1990[185]	Metoprolol	Aspirin	Medium	Yes	Not applicable	No	Low
Responder rate (Reduction in the number of migraine attacks greater than 50%)	Diener, 2001[188]	Metoprolol	Aspirin, 1500mg/day	Low	Yes	Not applicable	No	Low
Reduction of more than 50% in the number of migraine days	Louis, 1985[183]	Metoprolol	Clonidine	Medium	Yes	Not applicable	No	Low

Appendix Table D81. Comparative effectiveness of beta-blockers on migraine frequency, severity, and impact (results from randomized controlled clinical trials)

Definition of the Outcome	Reference Risk of Bias	Active Drug Dose	Control Drug, Dose	Randomized to Active/Control Drug	Mean [Standard Deviation] with Active Drug	Mean [Standard Deviation] with Control Drug	Mean Difference (95% CI)
Number of attacks per 4 weeks	Worz, 1991[186] Medium	Bisoprolol 5 to 10mg once daily	Metoprolol 50 to 100mg twice daily	78/78	Not reported	Not reported	0.1 (-0.2 to 0.4)
Mean frequency per 28 days in phase I	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	65/60	2.0 [1.7]	2.4 [2.0]	-0.4 (-1.0 to 0.3)
Mean frequency per 28 days in phase II	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	60/65	2.0 [1.7]	1.8 [1.7]	0.2 (-0.4 to 0.8)
Mean frequency per 28 days (overall)	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	125/125	2.0 [1.5]	2.1 [1.8]	-0.1 (-0.5 to 0.4)
Frequency of migraine attacks	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	1.3 [1.0]	1.6 [1.5]	-0.3 (-1.2 to 0.6)
Duration of migraine attacks at endpoint (hours)	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	26.0 [55.0]	15.0 [14.0]	11.0 (-18.6 to 40.6)
Severity at endpoint (measured on 100 mm visual analog scale)	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	54.0 [16.0]	50.0 [24.0]	4.0 (-10.4 to 18.4)
MIDAS: days with headache	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	13.0 [18.0]	14.0 [14.0]	-1.0 (-12.7 to 10.7)
MIDAS: pain intensity	Schellenberg, 2008[189]	Metoprolol Week 1: 47.5mg,	Nebivolol 5mg daily	14/16	6.0 [2.0]	6.0 [3.0]	0.0 (-1.8 to 1.8)

Appendix Table D81. Comparative effectiveness of beta-blockers on migraine frequency, severity, and impact (results from randomized controlled clinical trials)

Definition of the Outcome	Reference Risk of Bias	Active Drug Dose	Control Drug, Dose	Randomized to Active/Control Drug	Mean [Standard Deviation] with Active Drug	Mean [Standard Deviation] with Control Drug	Mean Difference (95% CI)
	Medium	week 2: 95mg, week 3 - 16:142.5mg					
Quality of life(SF-36): Physical	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	46.0 [7.0]	50.0 [10.0]	-4.0 (-10.1 to 2.1)
Quality of life(SF-36): Mental	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	14/16	48.0 [8.0]	45.0 [13.0]	3.0 (-4.6 to 10.6)
% change in frequency of migraine attacks	**Grotemeyer, 1990[185] Medium**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 1500mg/day**	**28/28**	**-50.0 [18.0]**	**-26.0 [22.0]**	**-24.0 (-34.5 to -13.5)**
Intensity of attacks	Grotemeyer, 1990[185] Medium	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 1500mg/day	28/28	1.6 [0.7]	1.4 [0.5]	0.2 (-0.1 to 0.5)
Frequency of migraine attacks	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 300mg/day**	**135/135**	**1.8 [1.6]**	**2.4 [1.9]**	**-0.5 (-1.0 to -0.1)**

Bold = significant differences at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D82. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials)

Definition of the Outcome	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group]	Events/ Randomized [Rate of Outcome in Control Group]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Reduction of frequency of attacks by more than 50%	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	11/125 [8.8]	12/125 [9.6]	0.9 (0.4 to 2.0)	-0.01 (-0.08 to 0.06)
Patients rated treatment as more effective	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	28/125 [22.4]	37/125 [29.6]	0.8 (0.5 to 1.2)	-0.07 (-0.18 to 0.04)
MIDAS :No impairment	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	2/16 [12.5]	1.1 (0.2 to 7.1)	0.02 (-0.23 to 0.26)
MIDAS :Severe impairment	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	5/16 [31.3]	0.5 (0.1 to 2.0)	-0.17 (-0.46 to 0.12)
MIDAS :Moderate impairment	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	4/14 [28.6]	6/16 [37.5]	0.8 (0.3 to 2.2)	-0.09 (-0.42 to 0.25)
MIDAS :Mild impairment	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	5/14 [35.7]	2/16 [12.5]	2.9 (0.7 to 12.5)	0.23 (-0.07 to 0.53)
Responder rate(at least 50% in number of attacks from baseline to endpoint)	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	8/14 [57.0]	8/16 [50.0]	1.1 (0.6 to 2.2)	0.07 (-0.29 to 0.43)

Appendix Table D82. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition of the Outcome	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group]	Events/ Randomized [Rate of Outcome in Control Group]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Patients using pain medications at endpoint	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 -16:142.5mg	Nebivolol 5mg daily	10/14 [71.4]	10/16 [62.5]	1.1 (0.7 to 1.9)	0.09 (-0.25 to 0.42)
Pain intensity: mild	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	6/135 [4.4]	9/135 [6.7]	0.7 (0.2 to 1.8)	-0.02 (-0.08 to 0.03)
Reduction of attacks more than 50%	**Grotemeyer, 1990[185] Medium**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 1500mg/day (**	**14/28 [50.0]**	**3/28 [10.7]**	**4.7 (1.5 to 14.5)**	**0.39 (0.18 to 0.61)**
Photophobia: mild	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	17/135 [12.6]	23/135 [17.0]	0.7 (0.4 to 1.3)	-0.04 (-0.13 to 0.04)
Phonophobia: mild	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	25/135 [18.5]	17/135 [12.6]	1.5 (0.8 to 2.6)	0.06 (-0.03 to 0.15)
Nausea: mild	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	33/135 [24.4]	22/135 [16.3]	1.5 (0.9 to 2.4)	0.08 (-0.01 to 0.18)

Appendix Table D82. Comparative effectiveness of beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Definition of the Outcome	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group]	Events/ Randomized [Rate of Outcome in Control Group]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Vomiting: mild	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	38/135 [28.1]	32/135 [23.7]	1.2 (0.8 to 1.8)	0.04 (-0.06 to 0.15)
Responder rate (Reduction in the number of migraine attacks greater than 50%)	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 300mg/day**	**40/135 [29.6]**	**61/135 [45.2]**	**0.7 (0.5 to 0.9)**	**-0.16 (-0.27 to -0.04)**
Reduction of more than 50% in the number of migraine days	Louis, 1985[183] Medium	Metoprolol 50mg BID	Clonidine 50µg BID	10/31 [32.3]	8/31 [25.8]	1.3 (0.6 to 2.7)	0.06 (-0.16 to 0.29)
Migraine days with nausea symptoms	Louis, 1985[183] Medium	Metoprolol 50mg BID	Clonidine 50µg BID	11/31 [35.0]	12/31 [39.0]	0.9 (0.5 to 1.8)	-0.03 (-0.27 to 0.21)
Migraine attacks accompanied by visual disturbances	Louis, 1985[183] Medium	Metoprolol 50mg BID	Clonidine 50µg BID	12/31 [38.7]	17/31 [54.8]	0.7 (0.4 to 1.2)	-0.16 (-0.41 to 0.08)
Subjective therapeutic evaluation: Marked or moderate	Louis, 1985[183] Medium	Metoprolol 50mg BID	Clonidine 50µg BID	22/31 [71.0]	15/31 [48.4]	1.5 (1.0 to 2.2)	0.23 (-0.01 to 0.46)
Number of migraine days reduced	**Louis, 1985[183] Medium**	**Metoprolol 50mg BID**	**Clonidine 50µg BID**	**24/31 [77.4]**	**14/31 [45.2]**	**1.7 (1.1 to 2.6)**	**0.32 (0.09 to 0.55)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D83. Exploratory Network Bayesian Meta-analysis of clinical response (defined as ≥50% reduction in migraine or self reported substantial reduction in monthly migraine frequency) with preventive approved drugs and off label drug classes in adults, results from randomized controlled clinical trials

Active Class	Control Class	Active Drug	Control Drugs	Risk of Bias, Reference	Events/ Randomized In Active Group	Events/Randomized in Control Group	Events/Randomized in the Second control Group
Placebo	Beta-blocker	Placebo	Propranolol	Medium[50]	17/83	34/83	NA/1
Anti-epileptic	Antidepressant	Topiramate	Amitriptyline	Low[172]	99/178	78/169	NA/1
Anti-epileptic	Anti-epileptic	Topiramate	Levetiracetam	Medium[168]	8/13	8/15	NA/1
Anti-epileptic	Anti-epileptic	Topiramate	Valproate	High[166]	20/22	21/22	NA/1
Anti-epileptic	Beta-blocker	Divalproex	Propranolol	High[68]	24/37	25/37	NA/1
Anti-epileptic	Other	Valproate	Cinnarizine	Low[190]	37/58	41/67	NA/1
Anti-epileptic	Other	Topiramate	Histamine	Low[169]	27/45	30/45	NA/1
Anti-epileptic	Other	Topiramate	Zonisamide	Medium[173]	16/40	15/40	NA/1
Beta-blocker	Anti-adrenergic	Metoprolol	Clonidine	Medium[183]	10/31	8/31	NA/1
Beta-blocker	Anti-adrenergic	Propranolol	Clonidine	Medium[69]	13/23	8/23	NA/1
Beta-blocker	Antidepressant	Propranolol	Amitriptyline	Medium[76]	12/54	10/54	NA/1
Beta-blocker	Antidepressant	Propranolol	Femoxetine	Medium[77]	3/15	1/14	NA/1
Beta-blocker	Antidepressant	Propranolol	Femoxetine	Medium[77]	1/13	3/11	NA/1
Beta-blocker	Antidepressant	Propranolol	Nortriptyline	Medium[75]	11/25	7/24	NA/1
Beta-blocker	Beta-blocker	Propranolol	Metoprolol	Medium[70]	15/36	17/36	NA/1
Beta-blocker	Beta-blocker Ca++ blocker	Propranolol	Metoprolol, Nifedipine	Medium[71]	0/19	6/22	0/17
Beta-blocker	Beta-blocker	Propranolol	Nadolol	Medium[73, 191]	9/15	5/13	NA/1
Beta-blocker	Beta-blocker	Propranolol	Nadolol	Medium[191]	5/44	18/47	NA/1
Beta-blocker	Calcium Channel Blockers	Propranolol	Nifedipine	High[74]	12/20	6/20	NA/1
Beta-blocker	Other	Propranolol	Cinnarizine	Low[73]	1/14	2/14	NA/1
NSAID	Beta-blocker	Aspirin	Metoprolol	Medium[185]	3/28	14/28	NA/1
NSAID	Beta-blocker	Aspirin	Metoprolol	Low[188]	61/135	40/135	NA/1
Placebo	ACE Inhibitors	Placebo	Captopril	Low[137]	0/12	8/12	NA/1
Placebo	ACE Inhibitors	Placebo	Lisinopril	Low[136]	0/60	14/60	NA/1
Placebo	Anti-adrenergic	Placebo	Clonidine	Medium[143]	0/30	10/30	NA/1
Placebo	Antidepressant	Placebo	Amitriptyline	Medium[103]	18/61	26/55	NA/1
Placebo	Antidepressant	Placebo	Amitriptyline	Medium[111]	48/197	47/194	NA/1
Placebo	Antidepressant	Placebo	Amitriptyline	Medium[112]	7/36	16/37	NA/1
Placebo	Antidepressant	Placebo	Fluoxetine	Medium[116]	1/16	6/16	NA/1
Placebo	Antidepressant	Placebo	Venlafaxine	Medium[122]	0/19	9/21	NA/1
Placebo	Anti-epileptic	Placebo	Acetazolamide	Low[80]	9/27	8/26	NA/1

Appendix Table D83. Exploratory Network Bayesian Meta-analysis of clinical response (defined as ≥50% reduction in migraine or self reported substantial reduction in monthly migraine frequency) with preventive approved drugs and off label drug classes in adults, results from randomized controlled clinical trials (continued)

Active Class	Control Class	Active Drug	Control Drugs	Risk of Bias, Reference	Events/ Randomized In Active Group	Events/Randomized in Control Group	Events/Randomized in the Second control Group
Placebo	Anti-epileptic	Placebo	Carbamazepin	Medium[86]	5/48	26/48	NA/1
Placebo	Anti-epileptic	Placebo	Divalproex	Medium[45]	5/37	33/70	NA/1
Placebo	Anti-epileptic	Placebo	Divalproex	Low[47]	2/15	19/44	NA/1
Placebo	Anti-epileptic	Placebo	Divalproex	Low[46]	32/116	50/123	NA/1
Placebo	Anti-epileptic	Placebo	Gabapentin	Medium[84]	12/22	18/23	NA/1
Placebo	Anti-epileptic	Placebo	Gabapentin	Medium[81]	5/45	26/98	NA/1
Placebo	Anti-epileptic	Placebo	Gabapentin	Low[192]	10/20	40/62	NA/1
Placebo	Anti-epileptic	Placebo	Oxcarbazepine	Low[83]	31/85	28/85	NA/1
Placebo	Anti-epileptic	Placebo	Valproate	Medium[49]	6/43	17/43	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Medium[31]	8/36	58/112	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Low[33]	16/372	8/384	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Low[41]	50/163	64/165	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Low[18]	2/21	5/19	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Low[20]	1/14	10/14	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Medium[24]	12/57	37/58	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Low[25]	93/372	188/386	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Medium[29]	25/73	55/140	NA/1
Placebo	Anti-epileptic	Placebo	Topiramate	Medium[34]	0/27	7/32	NA/1
Placebo	Anti-epileptic Beta-blocker	Placebo	Topiramate, propranolol	Low[43]	11/49	50/144	62/144
Placebo	Anti-epileptic	Placebo	Topiramate, lamotrigine	Low[44]	18/60	38/60	28/60
Placebo	Angiotensin II Antagonists	Placebo	Candesartan	Low[138]	2/60	23/60	NA/1
Placebo	Angiotensin II Antagonists	Placebo	Telmisartan	High[139]	11/47	16/48	NA/1
Placebo	Beta-blocker	Placebo	Acebutolol	Medium[91]	2/43	13/43	NA/1
Placebo	Beta-blocker	Placebo	Alprenolol	Medium[90]	12/33	11/33	NA/1
Placebo	Beta-blocker	Placebo	Atenolol	Medium[95]	0/24	8/24	NA/1
Placebo	Beta-blocker	Placebo	Metoprolol	Medium[100]	16/77	29/77	NA/1
Placebo	Beta-blocker	Placebo	Metoprolol	Medium[97]	4/37	10/34	NA/1
Placebo	Beta-blocker	Placebo	Nadolol	Low[98]	0/8	6/24	NA/1
Placebo	Beta-blocker	Placebo	Pindolol	Medium[89]	0/28	3/28	NA/1
Placebo	Beta-blocker Antiadrenergic	Placebo	Practolol, clonidine	Unclear[150]	13/50	21/50	22/50

Appendix Table D83. Exploratory Network Bayesian Meta-analysis of clinical response (defined as ≥50% reduction in migraine or self reported substantial reduction in monthly migraine frequency) with preventive approved drugs and off label drug classes in adults, results from randomized controlled clinical trials (continued)

Active Class	Control Class	Active Drug	Control Drugs	Risk of Bias, Reference	Events/ Randomized In Active Group	Events/Randomized in Control Group	Events/Randomized in the Second control Group
Placebo	Beta-blocker	Placebo	Propranolol, Timolol	Medium[60]	12/48	48/96	44/96
Placebo	Beta-blocker	Placebo	Propranolol	Medium[65]	0/11	5/8	NA/1
Placebo	Beta-blocker	Placebo	Propranolol, Timolol	Medium[61]	3/13	13/25	14/25
Placebo	Beta-blocker	Placebo	Propranolol	Low[193]	6/16	18/53	NA/1
Placebo	Beta-blocker	Placebo	Timolol	Medium[92]	0/14	2/14	NA/1
Placebo	Beta-blocker	Placebo	Timolol	Medium[79]	10/47	25/47	NA/1
Placebo	Calcium Channel Blockers	Placebo	Nifedipine	Medium[135]	4/36	20/36	NA/1
Placebo	Calcium Channel Blockers	Placebo	Nimodipine	Medium[132]	0/33	10/33	NA/1
Placebo	Calcium Channel Blockers	Placebo	Nimodipine	Medium[127]	4/30	8/30	NA/1
Placebo	Ergot alkaloid	Placebo	Dihydroergotamine	Low[155]	112/200	112/184	NA/1
Placebo	Ergot alkaloid	Placebo	Lisuride	Medium[158]	19/75	28/75	NA/1
Placebo	Magnesium	Placebo	Magnesium	Low[194]	10/34	10/35	NA/1
Placebo	Magnesium	Placebo	Magnesium	Low[195]	7/32	14/36	NA/1
Placebo	NSAID	Placebo	Aspirin	Low[196]	818/11034	661/11037	NA/1
Placebo	NSAID	Placebo	Aspirin	Medium[197]	1/40	17/40	NA/1
Placebo	NSAID	Placebo	Fenoprofen	Low[198]	11/35	10/38	NA/1
Placebo	NSAID	Placebo	Flurbiprofen	Medium[199]	7/23	16/23	NA/1
Placebo	NSAID	Placebo	Indomethacin	Medium [200]	5/19	6/19	NA/1
Placebo	NSAID	Placebo	Rofecoxib	Medium[201]	8/84	20/91	NA/1
Placebo	NSAID	Placebo	Tolfenamic Acid	Medium[202]	2/31	14/31	NA/1
Placebo	Other	Placebo	Montelukast	Low[203]	18/84	23/93	NA/1
Placebo	Other	Placebo	Tonabersat	Low[121]	24/65	24/59	NA/1

NA = Not available from 2 arms trials

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Divalproex[45-47]	Topiramate[18, 20, 24, 25, 29, 31, 44]	3.2 (1.3 to 7.5)	3.4 (2.1 to 5.6)	0.9 (0.3 to 2.5)	Medium
Propranolol[43, 50, 60, 61]	Topiramate[18, 20, 24, 25, 29, 31, 44]	2.8 (1.9 to 4.2)	3.4 (2.1 to 5.6)	0.8 (0.4 to 1.6)	Medium
Timolol[60, 61, 79]	Topiramate[18, 20, 24, 25, 29, 31, 44]	3.3 (1.9 to 5.6)	3.4 (2.1 to 5.6)	1.0 (0.5 to 2.0)	Medium
Valproate[49]	Topiramate[18, 20, 24, 25, 29, 31, 44]	4.0 (1.4 to 11.6)	3.4 (2.1 to 5.6)	1.2 (0.4 to 3.8)	Medium
Valproate[49]	Divalproex[45-47]	4.0 (1.4 to 11.6)	3.2 (1.3 to 7.5)	1.3 (0.3 to 5.0)	Medium
Divalproex[45-47]	Propranolol[43, 50, 60, 61]	3.2 (1.3 to 7.5)	2.8 (1.9 to 4.2)	1.1 (0.4 to 2.9)	Medium
Valproate[49]	Propranolol[43, 50, 60, 61]	4.0 (1.4 to 11.6)	2.8 (1.9 to 4.2)	1.4 (0.5 to 4.5)	Medium
Divalproex[45-47]	Timolol[60, 61, 79]	3.2 (1.3 to 7.5)	3.3 (1.9 to 5.6)	1.0 (0.4 to 2.7)	Medium
Propranolol[43, 50, 60, 61]	Timolol[60, 61, 79]	2.8 (1.9 to 4.2)	3.3 (1.9 to 5.6)	0.9 (0.4 to 1.7)	Medium
Valproate[49]	Timolol[60, 61, 79]	4.0 (1.4 to 11.6)	3.3 (1.9 to 5.6)	1.2 (0.4 to 4.1)	Medium
Divalproex[45-47]	Magnesium[194, 195]	3.2 (1.3 to 7.5)	1.5 (0.6 to 3.4)	2.2 (0.6 to 7.2)	Medium
Valproate[49]	Magnesium[194, 195]	4.0 (1.4 to 11.6)	1.5 (0.6 to 3.4)	2.8 (0.7 to 10.7)	Medium
Divalproex[45-47]	Gabapentin[81, 84, 192]	3.2 (1.3 to 7.5)	2.4 (1.3 to 4.6)	1.3 (0.4 to 3.8)	Medium
Valproate[49]	Gabapentin[81, 84, 192]	4.0 (1.4 to 11.6)	2.4 (1.3 to 4.6)	1.7 (0.5 to 5.7)	Medium
Divalproex[45-47]	Nimodipine[127, 132]	3.2 (1.3 to 7.5)	6.0 (0.5 to 66.2)	0.5 (0.0 to 6.7)	Medium
Valproate[49]	Nimodipine[127, 132]	4.0 (1.4 to 11.6)	6.0 (0.5 to 66.2)	0.7 (0.0 to 9.2)	Medium
Telmisartan[139]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.6 (0.7 to 4.0)	3.4 (2.1 to 5.6)	0.5 (0.2 to 1.4)	High
Telmisartan[139]	Divalproex[45, 46]	1.6 (0.7 to 4.0)	3.2 (1.3 to 7.5)	0.5 (0.1 to 1.8)	High
Telmisartan[139]	Propranolol[43, 50, 60, 61]	1.6 (0.7 to 4.0)	2.8 (1.9 to 4.2)	0.6 (0.2 to 1.6)	High
Telmisartan[139]	Timolol[60, 61, 79]	1.6 (0.7 to 4.0)	3.3 (1.9 to 5.6)	0.5 (0.2 to 1.4)	High
Telmisartan[139]	Valproate[49]	1.6 (0.7 to 4.0)	4.0 (1.4 to 11.6)	0.4 (0.1 to 1.6)	High
Candesartan[138]	Topiramate[18, 20, 24, 25, 29, 31, 44]	18.0 (4.0 to 81.0)	3.4 (2.1 to 5.6)	5.3 (1.1 to 26.0)	Low
Dihydroergotamine[155]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.2 (0.8 to 1.8)	3.4 (2.1 to 5.6)	0.4 (0.2 to 0.7)	Low
Lamotrigine[44]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.8 (0.8 to 3.7)	3.4 (2.1 to 5.6)	0.5 (0.2 to 1.3)	Low
Lisinopril[136]	Topiramate[18, 20, 24, 25, 29, 31, 44]	37.7 (2.2 to 649.0)	3.4 (2.1 to 5.6)	11.2 (0.6 to 200.5)	Low
Magnesium[194, 195]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.5 (0.6 to 3.4)	3.4 (2.1 to 5.6)	0.4 (0.2 to 1.2)	Low
Montelukast[203]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.2 (0.6 to 2.4)	3.4 (2.1 to 5.6)	0.4 (0.2 to 0.8)	Low
Nadolol[98]	Topiramate[18, 20, 24, 25, 29, 31, 44]	6.0 (0.3 to 118.6)	3.4 (2.1 to 5.6)	1.8 (0.1 to 36.6)	Low
Tonabersat[121]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.2 (0.6 to 2.4)	3.4 (2.1 to 5.6)	0.3 (0.1 to 0.8)	Low
Candesartan[138]	Divalproex[45-47]	18.0 (4.0 to 81.0)	3.2 (1.3 to 7.5)	5.7 (1.0 to 32.2)	Medium
Dihydroergotamine[155]	Divalproex[45-47]	1.2 (0.8 to 1.8)	3.2 (1.3 to 7.5)	0.4 (0.1 to 1.0)	Medium
Lamotrigine[44]	Divalproex[45-47]	1.8 (0.8 to 3.7)	3.2 (1.3 to 7.5)	0.6 (0.2 to 1.7)	Medium
Lisinopril[136]	Divalproex[45-47]	37.7 (2.2 to 649.0)	3.2 (1.3 to 7.5)	11.9 (0.6 to 233.2)	Medium
Montelukast[203]	Divalproex[45-47]	1.2 (0.6 to 2.4)	3.2 (1.3 to 7.5)	0.4 (0.1 to 1.2)	Medium
Nadolol[98]	Divalproex[45-47]	6.0 (0.3 to 118.6)	3.2 (1.3 to 7.5)	1.9 (0.1 to 42.4)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Tonabersat[121]	Divalproex[45-47]	1.2 (0.6 to 2.4)	3.2 (1.3 to 7.5)	0.4 (0.1 to 1.1)	Medium
Candesartan[138]	Propranolol[43, 50, 60, 61]	18.0 (4.0 to 81.0)	2.8 (1.9 to 4.2)	6.4 (1.4 to 30.4)	Medium
Dihydroergotamine[155]	Propranolol[43, 50, 60, 61]	1.2 (0.8 to 1.8)	2.8 (1.9 to 4.2)	0.4 (0.2 to 0.8)	Medium
Lamotrigine[44]	Propranolol[43, 50, 60, 61]	1.8 (0.8 to 3.7)	2.8 (1.9 to 4.2)	0.6 (0.3 to 1.4)	Medium
Lisinopril[136]	Propranolol[43, 50, 60, 61]	37.7 (2.2 to 649.0)	2.8 (1.9 to 4.2)	13.4 (0.8 to 237.7)	Medium
Magnesium[194, 195]	Propranolol[43, 50, 60, 61]	1.5 (0.6 to 3.4)	2.8 (1.9 to 4.2)	0.5 (0.2 to 1.3)	Medium
Montelukast[203]	Propranolol[43, 50, 60, 61]	1.2 (0.6 to 2.4)	2.8 (1.9 to 4.2)	0.4 (0.2 to 1.0)	Medium
Nadolol[98]	Propranolol[43, 50, 60, 61]	6.0 (0.3 to 118.6)	2.8 (1.9 to 4.2)	2.1 (0.1 to 43.4)	Medium
Tonabersat[121]	Propranolol[43, 50, 60, 61]	1.2 (0.6 to 2.4)	2.8 (1.9 to 4.2)	0.4 (0.2 to 1.0)	Medium
Candesartan[138]	Timolol[60, 61, 79]	18.0 (4.0 to 81.0)	3.3 (1.9 to 5.6)	5.5 (1.1 to 27.3)	Medium
Dihydroergotamine[155]	Timolol[60, 61, 79]	1.2 (0.8 to 1.8)	3.3 (1.9 to 5.6)	0.4 (0.2 to 0.7)	Medium
Lamotrigine[44]	Timolol[60, 61, 79]	1.8 (0.8 to 3.7)	3.3 (1.9 to 5.6)	0.5 (0.2 to 1.3)	Medium
Lisinopril[136]	Timolol[60, 61, 79]	37.7 (2.2 to 649.0)	3.3 (1.9 to 5.6)	11.6 (0.6 to 209.6)	Medium
Magnesium[194, 195]	Timolol[60, 61, 79]	1.5 (0.6 to 3.4)	3.3 (1.9 to 5.6)	0.4 (0.2 to 1.2)	Medium
Montelukast[203]	Timolol[60, 61, 79]	1.2 (0.6 to 2.4)	3.3 (1.9 to 5.6)	0.4 (0.2 to 0.9)	Medium
Nadolol[98]	Timolol[60, 61, 79]	6.0 (0.3 to 118.6)	3.3 (1.9 to 5.6)	1.8 (0.1 to 38.2)	Medium
Tonabersat[121]	Timolol[60, 61, 79]	1.2 (0.6 to 2.4)	3.3 (1.9 to 5.6)	0.4 (0.1 to 0.9)	Medium
Candesartan[138]	Valproate[49]	18.0 (4.0 to 81.0)	4.0 (1.4 to 11.6)	4.5 (0.7 to 28.1)	Medium
Dihydroergotamine[155]	Valproate[49]	1.2 (0.8 to 1.8)	4.0 (1.4 to 11.6)	0.3 (0.1 to 0.9)	Medium
Lamotrigine[44]	Valproate[49]	1.8 (0.8 to 3.7)	4.0 (1.4 to 11.6)	0.4 (0.1 to 1.6)	Medium
Lisinopril[136]	Valproate[49]	37.7 (2.2 to 649.0)	4.0 (1.4 to 11.6)	9.4 (0.4 to 194.7)	Medium
Montelukast[203]	Valproate[49]	1.2 (0.6 to 2.4)	4.0 (1.4 to 11.6)	0.3 (0.1 to 1.1)	Medium
Nadolol[98]	Valproate[49]	6.0 (0.3 to 118.6)	4.0 (1.4 to 11.6)	1.5 (0.1 to 35.3)	Medium
Tonabersat[121]	Valproate[49]	1.2 (0.6 to 2.4)	4.0 (1.4 to 11.6)	0.3 (0.1 to 1.0)	Medium
Acebutolol[91]	Topiramate[18, 20, 24, 25, 29, 31, 44]	8.9 (1.9 to 42.3)	3.4 (2.1 to 5.6)	2.6 (0.5 to 13.5)	Medium
Amitriptyline[112]	Topiramate[18, 20, 24, 25, 29, 31, 44]	3.2 (1.1 to 9.0)	3.4 (2.1 to 5.6)	0.9 (0.3 to 3.0)	Medium
Atenolol[95]	Topiramate[18, 20, 24, 25, 29, 31, 44]	25.2 (1.4 to 467.9)	3.4 (2.1 to 5.6)	7.5 (0.4 to 144.4)	Medium
Flurbiprofen[199]	Topiramate[18, 20, 24, 25, 29, 31, 44]	5.2 (1.5 to 18.3)	3.4 (2.1 to 5.6)	1.5 (0.4 to 6.0)	Medium
Gabapentin[81, 84, 192]	Topiramate[18, 20, 24, 25, 29, 31, 44]	2.4 (1.3 to 4.6)	3.4 (2.1 to 5.6)	0.7 (0.3 to 1.6)	Medium
Indomethacin[200]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.3 (0.3 to 5.3)	3.4 (2.1 to 5.6)	0.4 (0.1 to 1.7)	Medium
Lisuride[158]	Topiramate[18, 20, 24, 25, 29, 31, 44]	1.8 (0.9 to 3.5)	3.4 (2.1 to 5.6)	0.5 (0.2 to 1.2)	Medium
Nifedipine[135]	Topiramate[18, 20, 24, 25, 29, 31, 44]	10.0 (2.9 to 34.2)	3.4 (2.1 to 5.6)	3.0 (0.8 to 11.2)	Medium
Nimodipine[127, 132]	Topiramate[18, 20, 24, 25, 29, 31, 44]	6.0 (0.5 to 66.2)	3.4 (2.1 to 5.6)	1.8 (0.2 to 20.6)	Medium
Rofecoxib[201]	Topiramate[18, 20, 24, 25, 29, 31, 44]	2.7 (1.1 to 6.5)	3.4 (2.1 to 5.6)	0.8 (0.3 to 2.2)	Medium
Tolfenamic Acid[202]	Topiramate[18, 20, 24, 25, 29, 31, 44]	11.9 (2.4 to 59.0)	3.4 (2.1 to 5.6)	3.5 (0.7 to 18.8)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Amitriptyline[112]	Divalproex[45-47]	3.2 (1.1 to 9.0)	3.2 (1.3 to 7.5)	1.0 (0.3 to 3.9)	Medium
Atenolol[95]	Divalproex[45-47]	25.2 (1.4 to 467.9)	3.2 (1.3 to 7.5)	8.0 (0.4 to 167.6)	Medium
Flurbiprofen[199]	Divalproex[45-47]	5.2 (1.5 to 18.3)	3.2 (1.3 to 7.5)	1.7 (0.4 to 7.6)	Medium
Indomethacin[200]	Divalproex[45-47]	1.3 (0.3 to 5.3)	3.2 (1.3 to 7.5)	0.4 (0.1 to 2.1)	Medium
Lisuride[158]	Divalproex[45-47]	1.8 (0.9 to 3.5)	3.2 (1.3 to 7.5)	0.6 (0.2 to 1.7)	Medium
Nifedipine[135]	Divalproex[45-47]	10.0 (2.9 to 34.2)	3.2 (1.3 to 7.5)	3.2 (0.7 to 14.2)	Medium
Rofecoxib[201]	Divalproex[45-47]	2.7 (1.1 to 6.5)	3.2 (1.3 to 7.5)	0.8 (0.2 to 2.9)	Medium
Tolfenamic Acid[202]	Divalproex[45-47]	11.9 (2.4 to 59.0)	3.2 (1.3 to 7.5)	3.8 (0.6 to 23.2)	Medium
Acebutolol[91]	Propranolol[43, 50, 60, 61]	8.9 (1.9 to 42.3)	2.8 (1.9 to 4.2)	3.2 (0.6 to 15.9)	Medium
Amitriptyline[112]	Propranolol[43, 50, 60, 61]	3.2 (1.1 to 9.0)	2.8 (1.9 to 4.2)	1.1 (0.4 to 3.5)	Medium
Atenolol[95]	Propranolol[43, 50, 60, 61]	25.2 (1.4 to 467.9)	2.8 (1.9 to 4.2)	9.0 (0.5 to 171.2)	Medium
Flurbiprofen[199]	Propranolol[43, 50, 60, 61]	5.2 (1.5 to 18.3)	2.8 (1.9 to 4.2)	1.9 (0.5 to 7.0)	Medium
Gabapentin[81, 84, 192]	Propranolol[43, 50, 60, 61]	2.4 (1.3 to 4.6)	2.8 (1.9 to 4.2)	0.9 (0.4 to 1.8)	Medium
Indomethacin[200]	Propranolol[43, 50, 60, 61]	1.3 (0.3 to 5.3)	2.8 (1.9 to 4.2)	0.5 (0.1 to 2.0)	Medium
Lisuride[158]	Propranolol[43, 50, 60, 61]	1.8 (0.9 to 3.5)	2.8 (1.9 to 4.2)	0.6 (0.3 to 1.4)	Medium
Nifedipine[135]	Propranolol[43, 50, 60, 61]	10.0 (2.9 to 34.2)	2.8 (1.9 to 4.2)	3.6 (1.0 to 13.0)	Medium
Nimodipine[127, 132]	Propranolol[43, 50, 60, 61]	6.0 (0.5 to 66.2)	2.8 (1.9 to 4.2)	2.1 (0.2 to 24.3)	Medium
Rofecoxib[201]	Propranolol[43, 50, 60, 61]	2.7 (1.1 to 6.5)	2.8 (1.9 to 4.2)	1.0 (0.4 to 2.5)	Medium
Tolfenamic Acid[202]	Propranolol[43, 50, 60, 61]	11.9 (2.4 to 59.0)	2.8 (1.9 to 4.2)	4.2 (0.8 to 22.1)	Medium
Acebutolol[91]	Timolol[60, 61, 79]	8.9 (1.9 to 42.3)	3.3 (1.9 to 5.6)	2.7 (0.5 to 14.2)	Medium
Amitriptyline[112]	Timolol[60, 61, 79]	3.2 (1.1 to 9.0)	3.3 (1.9 to 5.6)	1.0 (0.3 to 3.2)	Medium
Atenolol[95]	Timolol[60, 61, 79]	25.2 (1.4 to 467.9)	3.3 (1.9 to 5.6)	7.7 (0.4 to 150.9)	Medium
Flurbiprofen[199]	Timolol[60, 61, 79]	5.2 (1.5 to 18.3)	3.3 (1.9 to 5.6)	1.6 (0.4 to 6.3)	Medium
Gabapentin[81, 84, 192]	Timolol[60, 61, 79]	2.4 (1.3 to 4.6)	3.3 (1.9 to 5.6)	0.7 (0.3 to 1.7)	Medium
Indomethacin[200]	Timolol[60, 61, 79]	1.3 (0.3 to 5.3)	3.3 (1.9 to 5.6)	0.4 (0.1 to 1.8)	Medium
Lisuride[158]	Timolol[60, 61, 79]	1.8 (0.9 to 3.5)	3.3 (1.9 to 5.6)	0.5 (0.2 to 1.3)	Medium
Nifedipine[135]	Timolol[60, 61, 79]	10.0 (2.9 to 34.2)	3.3 (1.9 to 5.6)	3.1 (0.8 to 11.8)	Medium
Nimodipine[127, 132]	Timolol[60, 61, 79]	6.0 (0.5 to 66.2)	3.3 (1.9 to 5.6)	1.8 (0.2 to 21.6)	Medium
Rofecoxib[201]	Timolol[60, 61, 79]	2.7 (1.1 to 6.5)	3.3 (1.9 to 5.6)	0.8 (0.3 to 2.3)	Medium
Tolfenamic Acid[202]	Timolol[60, 61, 79]	11.9 (2.4 to 59.0)	3.3 (1.9 to 5.6)	3.7 (0.7 to 19.8)	Medium
Acebutolol[91]	Valproate[49]	8.9 (1.9 to 42.3)	4.0 (1.4 to 11.6)	2.2 (0.3 to 14.5)	Medium
Amitriptyline[112]	Valproate[49]	3.2 (1.1 to 9.0)	4.0 (1.4 to 11.6)	0.8 (0.2 to 3.5)	Medium
Atenolol[95]	Valproate[49]	25.2 (1.4 to 467.9)	4.0 (1.4 to 11.6)	6.3 (0.3 to 139.7)	Medium
Flurbiprofen[199]	Valproate[49]	5.2 (1.5 to 18.3)	4.0 (1.4 to 11.6)	1.3 (0.3 to 6.7)	Medium
Indomethacin[200]	Valproate[49]	1.3 (0.3 to 5.3)	4.0 (1.4 to 11.6)	0.3 (0.1 to 1.9)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Lisuride[158]	Valproate[49]	1.8 (0.9 to 3.5)	4.0 (1.4 to 11.6)	0.4 (0.1 to 1.5)	Medium
Nifedipine[135]	Valproate[49]	10.0 (2.9 to 34.2)	4.0 (1.4 to 11.6)	2.5 (0.5 to 12.6)	Medium
Rofecoxib[201]	Valproate[49]	2.7 (1.1 to 6.5)	4.0 (1.4 to 11.6)	0.7 (0.2 to 2.6)	Medium
Tolfenamic Acid[202]	Valproate[49]	11.9 (2.4 to 59.0)	4.0 (1.4 to 11.6)	3.0 (0.4 to 20.1)	Medium
Clonidine[150]	Topiramate[18, 20, 24, 25, 29, 31, 44]	2.2 (1.0 to 5.2)	3.4 (2.1 to 5.6)	0.7 (0.2 to 1.8)	Medium
Clonidine[150]	Divalproex[45-47]	2.2 (1.0 to 5.2)	3.2 (1.3 to 7.5)	0.7 (0.2 to 2.4)	Medium
Clonidine[150]	Propranolol[43, 50, 60, 61]	2.2 (1.0 to 5.2)	2.8 (1.9 to 4.2)	0.8 (0.3 to 2.0)	Medium
Clonidine[150]	Timolol[60, 61, 79]	2.2 (1.0 to 5.2)	3.3 (1.9 to 5.6)	0.7 (0.3 to 1.9)	Medium
Clonidine[150]	Valproate[49]	2.2 (1.0 to 5.2)	4.0 (1.4 to 11.6)	0.6 (0.1 to 2.1)	Medium
Telmisartan[139]	Magnesium[194, 195]	1.6 (0.7 to 4.0)	1.5 (0.6 to 3.4)	1.1 (0.3 to 3.9)	High
Telmisartan[139]	Tonabersat[121]	1.6 (0.7 to 4.0)	1.2 (0.6 to 2.4)	1.4 (0.4 to 4.4)	High
Telmisartan[139]	Gabapentin[81, 84, 192]	1.6 (0.7 to 4.0)	2.4 (1.3 to 4.6)	0.7 (0.2 to 2.0)	High
Telmisartan[139]	Nimodipine[127, 132]	1.6 (0.7 to 4.0)	6.0 (0.5 to 66.2)	0.3 (0.0 to 3.5)	High
Telmisartan[139]	Tolfenamic Acid[202]	1.6 (0.7 to 4.0)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.9)	High
Candesartan[138]	Telmisartan[139]	18.0 (4.0 to 81.0)	1.6 (0.7 to 4.0)	11.0 (1.9 to 63.6)	High
Dihydroergotamine[155]	Telmisartan[139]	1.2 (0.8 to 1.8)	1.6 (0.7 to 4.0)	0.7 (0.3 to 2.0)	High
Lamotrigine[44]	Telmisartan[139]	1.8 (0.8 to 3.7)	1.6 (0.7 to 4.0)	1.1 (0.3 to 3.4)	High
Lisinopril[136]	Telmisartan[139]	37.7 (2.2 to 649.0)	1.6 (0.7 to 4.0)	23.1 (1.2 to 456.2)	High
Montelukast[203]	Telmisartan[139]	1.2 (0.6 to 2.4)	1.6 (0.7 to 4.0)	0.7 (0.2 to 2.3)	High
Nadolol[98]	Telmisartan[139]	6.0 (0.3 to 118.6)	1.6 (0.7 to 4.0)	3.7 (0.2 to 82.9)	High
Candesartan[138]	Dihydroergotamine[155]	18.0 (4.0 to 81.0)	1.2 (0.8 to 1.8)	14.7 (3.1 to 70.0)	Low
Candesartan[138]	Fenoprofen[198]	18.0 (4.0 to 81.0)	0.8 (0.3 to 2.2)	23.1 (3.8 to 141.8)	Low
Dihydroergotamine[155]	Fenoprofen[198]	1.2 (0.8 to 1.8)	0.8 (0.3 to 2.2)	1.6 (0.5 to 4.7)	Low
Candesartan[138]	Lamotrigine[44]	18.0 (4.0 to 81.0)	1.8 (0.8 to 3.7)	10.3 (1.9 to 55.0)	Low
Dihydroergotamine[155]	Lamotrigine[44]	1.2 (0.8 to 1.8)	1.8 (0.8 to 3.7)	0.7 (0.3 to 1.6)	Low
Candesartan[138]	Lisinopril[136]	18.0 (4.0 to 81.0)	37.7 (2.2 to 649.0)	0.5 (0.0 to 11.9)	Low
Dihydroergotamine[155]	Lisinopril[136]	1.2 (0.8 to 1.8)	37.7 (2.2 to 649.0)	0.0 (0.0 to 0.6)	Low
Lamotrigine[44]	Lisinopril[136]	1.8 (0.8 to 3.7)	37.7 (2.2 to 649.0)	0.0 (0.0 to 0.9)	Low
Candesartan[138]	Magnesium[194, 195]	18.0 (4.0 to 81.0)	1.5 (0.6 to 3.4)	12.3 (2.2 to 69.1)	Low
Dihydroergotamine[155]	Magnesium[194, 195]	1.2 (0.8 to 1.8)	1.5 (0.6 to 3.4)	0.8 (0.3 to 2.1)	Low
Lamotrigine[44]	Magnesium[194, 195]	1.8 (0.8 to 3.7)	1.5 (0.6 to 3.4)	1.2 (0.4 to 3.7)	Low
Lisinopril[136]	Magnesium[194, 195]	37.7 (2.2 to 649.0)	1.5 (0.6 to 3.4)	25.8 (1.3 to 501.9)	Low
Montelukast[203]	Magnesium[194, 195]	1.2 (0.6 to 2.4)	1.5 (0.6 to 3.4)	0.8 (0.3 to 2.5)	Low
Nadolol[98]	Magnesium[194, 195]	6.0 (0.3 to 118.6)	1.5 (0.6 to 3.4)	4.1 (0.2 to 91.2)	Low
Tonabersat[121]	Magnesium[194, 195]	1.2 (0.6 to 2.4)	1.5 (0.6 to 3.4)	0.8 (0.3 to 2.4)	Low

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Candesartan[138]	Montelukast[203]	18.0 (4.0 to 81.0)	1.2 (0.6 to 2.4)	15.0 (2.8 to 78.6)	Low
Dihydroergotamine[155]	Montelukast[203]	1.2 (0.8 to 1.8)	1.2 (0.6 to 2.4)	1.0 (0.5 to 2.3)	Low
Lamotrigine[44]	Montelukast[203]	1.8 (0.8 to 3.7)	1.2 (0.6 to 2.4)	1.5 (0.5 to 4.0)	Low
Lisinopril[136]	Montelukast[203]	37.7 (2.2 to 649.0)	1.2 (0.6 to 2.4)	31.3 (1.7 to 586.8)	Low
Candesartan[138]	Nadolol[98]	18.0 (4.0 to 81.0)	6.0 (0.3 to 118.6)	3.0 (0.1 to 85.6)	Low
Dihydroergotamine[155]	Nadolol[98]	1.2 (0.8 to 1.8)	6.0 (0.3 to 118.6)	0.2 (0.0 to 4.2)	Low
Lamotrigine[44]	Nadolol[98]	1.8 (0.8 to 3.7)	6.0 (0.3 to 118.6)	0.3 (0.0 to 6.4)	Low
Lisinopril[136]	Nadolol [98]	37.7 (2.2 to 649.0)	6.0 (0.3 to 118.6)	6.3 (0.1 to 391.4)	Low
Montelukast[203]	Nadolol[98]	1.2 (0.6 to 2.4)	6.0 (0.3 to 118.6)	0.2 (0.0 to 4.3)	Low
Candesartan[138]	Oxcarbazepine[83]	18.0 (4.0 to 81.0)	0.9 (0.5 to 1.6)	21.1 (4.1 to 107.5)	Low
Dihydroergotamine[155]	Oxcarbazepine[83]	1.2 (0.8 to 1.8)	0.9 (0.5 to 1.6)	1.4 (0.7 to 3.0)	Low
Lamotrigine[44]	Oxcarbazepine[83]	1.8 (0.8 to 3.7)	0.9 (0.5 to 1.6)	2.0 (0.8 to 5.4)	Low
Lisinopril[136]	Oxcarbazepine[83]	37.7 (2.2 to 649.0)	0.9 (0.5 to 1.6)	44.1 (2.4 to 813.0)	Low
Montelukast[203]	Oxcarbazepine[83]	1.2 (0.6 to 2.4)	0.9 (0.5 to 1.6)	1.4 (0.5 to 3.6)	Low
Nadolol[98]	Oxcarbazepine[83]	6.0 (0.3 to 118.6)	0.9 (0.5 to 1.6)	7.0 (0.3 to 148.1)	Low
Candesartan[138]	Tonabersat[121]	18.0 (4.0 to 81.0)	1.2 (0.6 to 2.4)	15.4 (2.9 to 81.6)	Low
Dihydroergotamine[155]	Tonabersat[121]	1.2 (0.8 to 1.8)	1.2 (0.6 to 2.4)	1.0 (0.5 to 2.4)	Low
Lamotrigine[44]	Tonabersat[121]	1.8 (0.8 to 3.7)	1.2 (0.6 to 2.4)	1.5 (0.5 to 4.2)	Low
Lisinopril[136]	Tonabersat[121]	37.7 (2.2 to 649.0)	1.2 (0.6 to 2.4)	32.2 (1.7 to 606.6)	Low
Montelukast[203]	Tonabersat[121]	1.2 (0.6 to 2.4)	1.2 (0.6 to 2.4)	1.0 (0.4 to 2.8)	Low
Nadolol[98]	Tonabersat[121]	6.0 (0.3 to 118.6)	1.2 (0.6 to 2.4)	5.1 (0.2 to 110.4)	Low
Candesartan[138]	Carbamazepine[86]	18.0 (4.0 to 81.0)	10.2 (3.4 to 30.1)	1.8 (0.3 to 11.3)	Medium
Candesartan[138]	Flurbiprofen[199]	18.0 (4.0 to 81.0)	5.2 (1.5 to 18.3)	3.5 (0.5 to 24.5)	Medium
Dihydroergotamine[155]	Flurbiprofen[199]	1.2 (0.8 to 1.8)	5.2 (1.5 to 18.3)	0.2 (0.1 to 0.9)	Medium
Candesartan[138]	Gabapentin[81, 84, 192]	18.0 (4.0 to 81.0)	2.4 (1.3 to 4.6)	7.4 (1.4 to 37.8)	Medium
Dihydroergotamine[155]	Gabapentin[81, 84, 192]	1.2 (0.8 to 1.8)	2.4 (1.3 to 4.6)	0.5 (0.2 to 1.1)	Medium
Lamotrigine[44]	Gabapentin[81, 84, 192]	1.8 (0.8 to 3.7)	2.4 (1.3 to 4.6)	0.7 (0.3 to 1.9)	Medium
Lisinopril[136]	Gabapentin[81, 84, 192]	37.7 (2.2 to 649.0)	2.4 (1.3 to 4.6)	15.5 (0.8 to 285.4)	Medium
Montelukast[203]	Gabapentin[81, 84, 192]	1.2 (0.6 to 2.4)	2.4 (1.3 to 4.6)	0.5 (0.2 to 1.3)	Medium
Nadolol[98]	Gabapentin[81, 84, 192]	6.0 (0.3 to 118.6)	2.4 (1.3 to 4.6)	2.4 (0.1 to 52.0)	Medium
Tonabersat[121]	Gabapentin[81, 84, 192]	1.2 (0.6 to 2.4)	2.4 (1.3 to 4.6)	0.5 (0.2 to 1.3)	Medium
Candesartan[138]	Indomethacin[200]	18.0 (4.0 to 81.0)	1.3 (0.3 to 5.3)	13.9 (1.8 to 109.3)	Medium
Dihydroergotamine[155]	Indomethacin[200]	1.2 (0.8 to 1.8)	1.3 (0.3 to 5.3)	0.9 (0.2 to 4.1)	Medium
Candesartan[138]	Lisuride[158]	18.0 (4.0 to 81.0)	1.8 (0.9 to 3.5)	10.3 (2.0 to 53.9)	Medium
Dihydroergotamine[155]	Lisuride[158]	1.2 (0.8 to 1.8)	1.8 (0.9 to 3.5)	0.7 (0.3 to 1.6)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Lamotrigine[44]	Lisuride[158]	1.8 (0.8 to 3.7)	1.8 (0.9 to 3.5)	1.0 (0.4 to 2.8)	Medium
Lisinopril[136]	Lisuride[158]	37.7 (2.2 to 649.0)	1.8 (0.9 to 3.5)	21.5 (1.1 to 402.3)	Medium
Candesartan[138]	Nifedipine[135]	18.0 (4.0 to 81.0)	10.0 (2.9 to 34.2)	1.8 (0.3 to 12.6)	Medium
Dihydroergotamine[155]	Nifedipine[135]	1.2 (0.8 to 1.8)	10.0 (2.9 to 34.2)	0.1 (0.0 to 0.4)	Medium
Lamotrigine[44]	Nifedipine[135]	1.8 (0.8 to 3.7)	10.0 (2.9 to 34.2)	0.2 (0.0 to 0.7)	Medium
Lisinopril[136]	Nifedipine[135]	37.7 (2.2 to 649.0)	10.0 (2.9 to 34.2)	3.8 (0.2 to 83.7)	Medium
Montelukast[203]	Nifedipine[135]	1.2 (0.6 to 2.4)	10.0 (2.9 to 34.2)	0.1 (0.0 to 0.5)	Medium
Nadolol[98]	Nifedipine[135]	6.0 (0.3 to 118.6)	10.0 (2.9 to 34.2)	0.6 (0.0 to 15.1)	Medium
Candesartan[138]	Nimodipine[127, 132]	18.0 (4.0 to 81.0)	6.0 (0.5 to 66.2)	3.0 (0.2 to 50.9)	Medium
Dihydroergotamine[155]	Nimodipine[127, 132]	1.2 (0.8 to 1.8)	6.0 (0.5 to 66.2)	0.2 (0.0 to 2.3)	Medium
Lamotrigine[44]	Nimodipine[127, 132]	1.8 (0.8 to 3.7)	6.0 (0.5 to 66.2)	0.3 (0.0 to 3.6)	Medium
Lisinopril[136]	Nimodipine[127, 132]	37.7 (2.2 to 649.0)	6.0 (0.5 to 66.2)	6.3 (0.2 to 259.5)	Medium
Magnesium[194, 195]	Nimodipine[127, 132]	1.5 (0.6 to 3.4)	6.0 (0.5 to 66.2)	0.2 (0.0 to 3.1)	Medium
Montelukast[203]	Nimodipine[127, 132]	1.2 (0.6 to 2.4)	6.0 (0.5 to 66.2)	0.2 (0.0 to 2.4)	Medium
Nadolol[98]	Nimodipine[127, 132]	6.0 (0.3 to 118.6)	6.0 (0.5 to 66.2)	1.0 (0.0 to 45.9)	Medium
Tonabersat[121]	Nimodipine[127, 132]	1.2 (0.6 to 2.4)	6.0 (0.5 to 66.2)	0.2 (0.0 to 2.4)	Medium
Candesartan[138]	Rofecoxib[201]	18.0 (4.0 to 81.0)	2.7 (1.1 to 6.5)	6.7 (1.2 to 38.5)	Medium
Dihydroergotamine[155]	Rofecoxib[201]	1.2 (0.8 to 1.8)	2.7 (1.1 to 6.5)	0.5 (0.2 to 1.2)	Medium
Lamotrigine[44]	Rofecoxib[201]	1.8 (0.8 to 3.7)	2.7 (1.1 to 6.5)	0.7 (0.2 to 2.1)	Medium
Lisinopril[136]	Rofecoxib[201]	37.7 (2.2 to 649.0)	2.7 (1.1 to 6.5)	14.1 (0.7 to 277.1)	Medium
Montelukast[203]	Rofecoxib[201]	1.2 (0.6 to 2.4)	2.7 (1.1 to 6.5)	0.5 (0.1 to 1.4)	Medium
Nadolol[98]	Rofecoxib[201]	6.0 (0.3 to 118.6)	2.7 (1.1 to 6.5)	2.2 (0.1 to 50.4)	Medium
Candesartan[138]	Tolfenamic Acid[202]	18.0 (4.0 to 81.0)	11.9 (2.4 to 59.0)	1.5 (0.2 to 13.5)	Medium
Dihydroergotamine[155]	Tolfenamic Acid[202]	1.2 (0.8 to 1.8)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.5)	Medium
Lamotrigine[44]	Tolfenamic Acid[202]	1.8 (0.8 to 3.7)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.9)	Medium
Lisinopril[136]	Tolfenamic Acid[202]	37.7 (2.2 to 649.0)	11.9 (2.4 to 59.0)	3.2 (0.1 to 82.6)	Medium
Montelukast[203]	Tolfenamic Acid[202]	1.2 (0.6 to 2.4)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.6)	Medium
Nadolol[98]	Tolfenamic Acid[202]	6.0 (0.3 to 118.6)	11.9 (2.4 to 59.0)	0.5 (0.0 to 14.8)	Medium
Candesartan[138]	Clonidine[150]	18.0 (4.0 to 81.0)	2.2 (1.0 to 5.2)	8.1 (1.4 to 45.2)	Medium
Acebutolol[91]	Telmisartan[139]	8.9 (1.9 to 42.3)	1.6 (0.7 to 4.0)	5.4 (0.9 to 33.0)	High
Amitriptyline[112]	Telmisartan[139]	3.2 (1.1 to 9.0)	1.6 (0.7 to 4.0)	1.9 (0.5 to 7.7)	High
Atenolol[95]	Telmisartan[139]	25.2 (1.4 to 467.9)	1.6 (0.7 to 4.0)	15.4 (0.7 to 327.8)	High
Flurbiprofen[199]	Telmisartan[139]	5.2 (1.5 to 18.3)	1.6 (0.7 to 4.0)	3.2 (0.7 to 15.0)	High
Indomethacin[200]	Telmisartan[139]	1.3 (0.3 to 5.3)	1.6 (0.7 to 4.0)	0.8 (0.1 to 4.2)	High
Lisuride[158]	Telmisartan[139]	1.8 (0.9 to 3.5)	1.6 (0.7 to 4.0)	1.1 (0.3 to 3.4)	High

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Nifedipine[135]	Telmisartan[139]	10.0 (2.9 to 34.2)	1.6 (0.7 to 4.0)	6.1 (1.3 to 28.1)	High
Rofecoxib[201]	Telmisartan[139]	2.7 (1.1 to 6.5)	1.6 (0.7 to 4.0)	1.6 (0.5 to 5.8)	High
Acebutolol[91]	Acetazolamide[80]	8.9 (1.9 to 42.3)	0.9 (0.3 to 2.8)	10.0 (1.4 to 69.7)	Medium
Acebutolol[91]	Aspirin[196]	8.9 (1.9 to 42.3)	0.8 (0.7 to 0.9)	11.2 (2.3 to 53.4)	Medium
Amitriptyline[112]	Aspirin[196]	3.2 (1.1 to 9.0)	0.8 (0.7 to 0.9)	4.0 (1.4 to 11.4)	Medium
Acebutolol[91]	Candesartan[138]	8.9 (1.9 to 42.3)	18.0 (4.0 to 81.0)	0.5 (0.1 to 4.3)	Medium
Amitriptyline[112]	Candesartan[138]	3.2 (1.1 to 9.0)	18.0 (4.0 to 81.0)	0.2 (0.0 to 1.1)	Medium
Atenolol[95]	Candesartan[138]	25.2 (1.4 to 467.9)	18.0 (4.0 to 81.0)	1.4 (0.1 to 37.3)	Medium
Acebutolol[91]	Dihydroergotamine[155]	8.9 (1.9 to 42.3)	1.2 (0.8 to 1.8)	7.3 (1.4 to 36.5)	Medium
Amitriptyline[112]	Dihydroergotamine[155]	3.2 (1.1 to 9.0)	1.2 (0.8 to 1.8)	2.6 (0.8 to 8.0)	Medium
Atenolol[95]	Dihydroergotamine[155]	25.2 (1.4 to 467.9)	1.2 (0.8 to 1.8)	20.7 (1.1 to 393.8)	Medium
Acebutolol[91]	Fenoprofen[198]	8.9 (1.9 to 42.3)	0.8 (0.3 to 2.2)	11.4 (1.8 to 73.4)	Medium
Amitriptyline[112]	Fenoprofen[198]	3.2 (1.1 to 9.0)	0.8 (0.3 to 2.2)	4.1 (0.9 to 17.5)	Medium
Atenolol[95]	Fenoprofen[198]	25.2 (1.4 to 467.9)	0.8 (0.3 to 2.2)	32.4 (1.5 to 712.7)	Medium
Acebutolol[91]	Lamotrigine[44]	8.9 (1.9 to 42.3)	1.8 (0.8 to 3.7)	5.1 (0.9 to 28.6)	Medium
Amitriptyline[112]	Lamotrigine[44]	3.2 (1.1 to 9.0)	1.8 (0.8 to 3.7)	1.8 (0.5 to 6.5)	Medium
Atenolol[95]	Lamotrigine[44]	25.2 (1.4 to 467.9)	1.8 (0.8 to 3.7)	14.4 (0.7 to 293.1)	Medium
Flurbiprofen[199]	Lamotrigine[44]	5.2 (1.5 to 18.3)	1.8 (0.8 to 3.7)	3.0 (0.7 to 12.8)	Medium
Indomethacin[200]	Lamotrigine[44]	1.3 (0.3 to 5.3)	1.8 (0.8 to 3.7)	0.7 (0.2 to 3.6)	Medium
Acebutolol[91]	Lisinopril[136]	8.9 (1.9 to 42.3)	37.7 (2.2 to 649.0)	0.2 (0.0 to 6.0)	Medium
Amitriptyline[112]	Lisinopril[136]	3.2 (1.1 to 9.0)	37.7 (2.2 to 649.0)	0.1 (0.0 to 1.7)	Medium
Atenolol[95]	Lisinopril[136]	25.2 (1.4 to 467.9)	37.7 (2.2 to 649.0)	0.7 (0.0 to 39.4)	Medium
Flurbiprofen[199]	Lisinopril[136]	5.2 (1.5 to 18.3)	37.7 (2.2 to 649.0)	0.1 (0.0 to 3.1)	Medium
Indomethacin[200]	Lisinopril[136]	1.3 (0.3 to 5.3)	37.7 (2.2 to 649.0)	0.0 (0.0 to 0.8)	Medium
Acebutolol[91]	Magnesium[194, 195]	8.9 (1.9 to 42.3)	1.5 (0.6 to 3.4)	6.1 (1.0 to 35.9)	Medium
Amitriptyline[112]	Magnesium[194, 195]	3.2 (1.1 to 9.0)	1.5 (0.6 to 3.4)	2.2 (0.6 to 8.3)	Medium
Atenolol[95]	Magnesium[194, 195]	25.2 (1.4 to 467.9)	1.5 (0.6 to 3.4)	17.3 (0.8 to 360.7)	Medium
Flurbiprofen[199]	Magnesium[194, 195]	5.2 (1.5 to 18.3)	1.5 (0.6 to 3.4)	3.6 (0.8 to 16.2)	Medium
Gabapentin[81, 84, 192]	Magnesium[194, 195]	2.4 (1.3 to 4.6)	1.5 (0.6 to 3.4)	1.7 (0.6 to 4.8)	Medium
Indomethacin[200]	Magnesium[194, 195]	1.3 (0.3 to 5.3)	1.5 (0.6 to 3.4)	0.9 (0.2 to 4.6)	Medium
Lisuride[158]	Magnesium[194, 195]	1.8 (0.9 to 3.5)	1.5 (0.6 to 3.4)	1.2 (0.4 to 3.6)	Medium
Nifedipine[135]	Magnesium[194, 195]	10.0 (2.9 to 34.2)	1.5 (0.6 to 3.4)	6.8 (1.5 to 30.4)	Medium
Rofecoxib[201]	Magnesium[194, 195]	2.7 (1.1 to 6.5)	1.5 (0.6 to 3.4)	1.8 (0.5 to 6.2)	Medium
Tolfenamic Acid[202]	Magnesium[194, 195]	11.9 (2.4 to 59.0)	1.5 (0.6 to 3.4)	8.2 (1.3 to 49.8)	Medium
Acebutolol[91]	Montelukast[203]	8.9 (1.9 to 42.3)	1.2 (0.6 to 2.4)	7.4 (1.3 to 40.9)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Amitriptyline[112]	Montelukast[203]	3.2 (1.1 to 9.0)	1.2 (0.6 to 2.4)	2.6 (0.7 to 9.3)	Medium
Atenolol[95]	Montelukast[203]	25.2 (1.4 to 467.9)	1.2 (0.6 to 2.4)	21.0 (1.0 to 422.1)	Medium
Flurbiprofen[199]	Montelukast[203]	5.2 (1.5 to 18.3)	1.2 (0.6 to 2.4)	4.3 (1.0 to 18.3)	Medium
Indomethacin[200]	Montelukast[203]	1.3 (0.3 to 5.3)	1.2 (0.6 to 2.4)	1.1 (0.2 to 5.2)	Medium
Lisuride[158]	Montelukast[203]	1.8 (0.9 to 3.5)	1.2 (0.6 to 2.4)	1.5 (0.5 to 3.9)	Medium
Acebutolol[91]	Nadolol[98]	8.9 (1.9 to 42.3)	6.0 (0.3 to 118.6)	1.5 (0.1 to 43.3)	Medium
Amitriptyline[112]	Nadolol[98]	3.2 (1.1 to 9.0)	6.0 (0.3 to 118.6)	0.5 (0.0 to 12.6)	Medium
Atenolol[95]	Nadolol[98]	25.2 (1.4 to 467.9)	6.0 (0.3 to 118.6)	4.2 (0.1 to 275.8)	Medium
Flurbiprofen[199]	Nadolol[98]	5.2 (1.5 to 18.3)	6.0 (0.3 to 118.6)	0.9 (0.0 to 22.4)	Medium
Indomethacin[200]	Nadolol[98]	1.3 (0.3 to 5.3)	6.0 (0.3 to 118.6)	0.2 (0.0 to 5.9)	Medium
Lisuride[158]	Nadolol[98]	1.8 (0.9 to 3.5)	6.0 (0.3 to 118.6)	0.3 (0.0 to 6.3)	Medium
Acebutolol [91]	Oxcarbazepine[83]	8.9 (1.9 to 42.3)	0.9 (0.5 to 1.6)	10.4 (1.9 to 56.0)	Medium
Amitriptyline[112]	Oxcarbazepine[83]	3.2 (1.1 to 9.0)	0.9 (0.5 to 1.6)	3.7 (1.1 to 12.6)	Medium
Atenolol[95]	Oxcarbazepine[83]	25.2 (1.4 to 467.9)	0.9 (0.5 to 1.6)	29.5 (1.5 to 585.1)	Medium
Flurbiprofen[199]	Oxcarbazepine[83]	5.2 (1.5 to 18.3)	0.9 (0.5 to 1.6)	6.1 (1.5 to 24.9)	Medium
Indomethacin[200]	Oxcarbazepine[83]	1.3 (0.3 to 5.3)	0.9 (0.5 to 1.6)	1.5 (0.3 to 7.1)	Medium
Lisuride[158]	Oxcarbazepine[83]	1.8 (0.9 to 3.5)	0.9 (0.5 to 1.6)	2.1 (0.8 to 5.3)	Medium
Nifedipine[135]	Oxcarbazepine[83]	10.0 (2.9 to 34.2)	0.9 (0.5 to 1.6)	11.7 (2.9 to 46.6)	Medium
Acebutolol[91]	Tonabersat[121]	8.9 (1.9 to 42.3)	1.2 (0.6 to 2.4)	7.6 (1.4 to 42.4)	Medium
Amitriptyline[112]	Tonabersat[121]	3.2 (1.1 to 9.0)	1.2 (0.6 to 2.4)	2.7 (0.8 to 9.7)	Medium
Atenolol[95]	Tonabersat[121]	25.2 (1.4 to 467.9)	1.2 (0.6 to 2.4)	21.5 (1.1 to 436.3)	Medium
Flurbiprofen[199]	Tonabersat[121]	5.2 (1.5 to 18.3)	1.2 (0.6 to 2.4)	4.5 (1.0 to 19.0)	Medium
Indomethacin[200]	Tonabersat[121]	1.3 (0.3 to 5.3)	1.2 (0.6 to 2.4)	1.1 (0.2 to 5.4)	Medium
Lisuride[158]	Tonabersat[121]	1.8 (0.9 to 3.5)	1.2 (0.6 to 2.4)	1.5 (0.5 to 4.1)	Medium
Nifedipine[135]	Tonabersat[121]	10.0 (2.9 to 34.2)	1.2 (0.6 to 2.4)	8.5 (2.0 to 35.6)	Medium
Rofecoxib[201]	Tonabersat[121]	2.7 (1.1 to 6.5)	1.2 (0.6 to 2.4)	2.3 (0.7 to 7.1)	Medium
Tolfenamic Acid[202]	Tonabersat[121]	11.9 (2.4 to 59.0)	1.2 (0.6 to 2.4)	10.2 (1.8 to 58.9)	Medium
Acebutolol[91]	Amitriptyline[112]	8.9 (1.9 to 42.3)	3.2 (1.1 to 9.0)	2.8 (0.4 to 18.5)	Medium
Acebutolol[91]	Atenolol[95]	8.9 (1.9 to 42.3)	0.9 (0.3 to 2.4)	10.2 (1.6 to 65.3)	Medium
Acebutolol[91]	Atenolol[95]	8.9 (1.9 to 42.3)	25.2 (1.4 to 467.9)	0.4 (0.0 to 9.6)	Medium
Amitriptyline[112]	Atenolol[95]	3.2 (1.1 to 9.0)	25.2 (1.4 to 467.9)	0.1 (0.0 to 2.8)	Medium
Acebutolol[91]	Carbamazepine[86]	8.9 (1.9 to 42.3)	10.2 (3.4 to 30.1)	0.9 (0.1 to 5.9)	Medium
Amitriptyline[112]	Carbamazepine[86]	3.2 (1.1 to 9.0)	10.2 (3.4 to 30.1)	0.3 (0.1 to 1.4)	Medium
Atenolol[95]	Carbamazepine[86]	25.2 (1.4 to 467.9)	10.2 (3.4 to 30.1)	2.5 (0.1 to 56.0)	Medium
Acebutolol[91]	Divalproex[45-47]	8.9 (1.9 to 42.3)	3.2 (1.3 to 7.5)	2.8 (0.5 to 16.7)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Acebutolol[91]	Flurbiprofen[199]	8.9 (1.9 to 42.3)	5.2 (1.5 to 18.3)	1.7 (0.2 to 12.6)	Medium
Amitriptyline[112]	Flurbiprofen[199]	3.2 (1.1 to 9.0)	5.2 (1.5 to 18.3)	0.6 (0.1 to 3.1)	Medium
Atenolol[95]	Flurbiprofen[199]	25.2 (1.4 to 467.9)	5.2 (1.5 to 18.3)	4.8 (0.2 to 116.0)	Medium
Acebutolol[91]	Gabapentin[81, 84, 192]	8.9 (1.9 to 42.3)	2.4 (1.3 to 4.6)	3.6 (0.7 to 19.6)	Medium
Amitriptyline[112]	Gabapentin[81, 84, 192]	3.2 (1.1 to 9.0)	2.4 (1.3 to 4.6)	1.3 (0.4 to 4.4)	Medium
Atenolol[95]	Gabapentin[81, 84, 192]	25.2 (1.4 to 467.9)	2.4 (1.3 to 4.6)	10.4 (0.5 to 205.4)	Medium
Flurbiprofen[199]	Gabapentin[81, 84, 192]	5.2 (1.5 to 18.3)	2.4 (1.3 to 4.6)	2.1 (0.5 to 8.7)	Medium
Indomethacin[200]	Gabapentin[81, 84, 192]	1.3 (0.3 to 5.3)	2.4 (1.3 to 4.6)	0.5 (0.1 to 2.5)	Medium
Lisuride[158]	Gabapentin[81, 84, 192]	1.8 (0.9 to 3.5)	2.4 (1.3 to 4.6)	0.7 (0.3 to 1.9)	Medium
Nifedipine[135]	Gabapentin[81, 84, 192]	10.0 (2.9 to 34.2)	2.4 (1.3 to 4.6)	4.1 (1.0 to 16.4)	Medium
Rofecoxib[201]	Gabapentin[81, 84, 192]	2.7 (1.1 to 6.5)	2.4 (1.3 to 4.6)	1.1 (0.4 to 3.2)	Medium
Tolfenamic Acid[202]	Gabapentin[81, 84, 192]	11.9 (2.4 to 59.0)	2.4 (1.3 to 4.6)	4.9 (0.9 to 27.3)	Medium
Acebutolol[91]	Indomethacin[200]	8.9 (1.9 to 42.3)	1.3 (0.3 to 5.3)	6.9 (0.8 to 56.2)	Medium
Amitriptyline[112]	Indomethacin[200]	3.2 (1.1 to 9.0)	1.3 (0.3 to 5.3)	2.4 (0.4 to 14.1)	Medium
Atenolol[95]	Indomethacin[200]	25.2 (1.4 to 467.9)	1.3 (0.3 to 5.3)	19.5 (0.8 to 499.2)	Medium
Flurbiprofen[199]	Indomethacin[200]	5.2 (1.5 to 18.3)	1.3 (0.3 to 5.3)	4.0 (0.6 to 26.6)	Medium
Acebutolol[91]	Lisuride[158]	8.9 (1.9 to 42.3)	1.8 (0.9 to 3.5)	5.1 (0.9 to 28.0)	Medium
Amitriptyline[112]	Lisuride[158]	3.2 (1.1 to 9.0)	1.8 (0.9 to 3.5)	1.8 (0.5 to 6.4)	Medium
Atenolol[95]	Lisuride[158]	25.2 (1.4 to 467.9)	1.8 (0.9 to 3.5)	14.4 (0.7 to 289.4)	Medium
Flurbiprofen[199]	Lisuride[158]	5.2 (1.5 to 18.3)	1.8 (0.9 to 3.5)	3.0 (0.7 to 12.5)	Medium
Indomethacin[200]	Lisuride[158]	1.3 (0.3 to 5.3)	1.8 (0.9 to 3.5)	0.7 (0.2 to 3.5)	Medium
Acebutolol[91]	Nifedipine[135]	8.9 (1.9 to 42.3)	10.0 (2.9 to 34.2)	0.9 (0.1 to 6.5)	Medium
Amitriptyline[112]	Nifedipine[135]	3.2 (1.1 to 9.0)	10.0 (2.9 to 34.2)	0.3 (0.1 to 1.6)	Medium
Atenolol[95]	Nifedipine[135]	25.2 (1.4 to 467.9)	10.0 (2.9 to 34.2)	2.5 (0.1 to 60.0)	Medium
Flurbiprofen[199]	Nifedipine[135]	5.2 (1.5 to 18.3)	10.0 (2.9 to 34.2)	0.5 (0.1 to 3.0)	Medium
Indomethacin[200]	Nifedipine[135]	1.3 (0.3 to 5.3)	10.0 (2.9 to 34.2)	0.1 (0.0 to 0.8)	Medium
Lisuride[158]	Nifedipine[135]	1.8 (0.9 to 3.5)	10.0 (2.9 to 34.2)	0.2 (0.0 to 0.7)	Medium
Acebutolol[91]	Nimodipine[127, 132]	8.9 (1.9 to 42.3)	6.0 (0.5 to 66.2)	1.5 (0.1 to 25.9)	Medium
Amitriptyline[112]	Nimodipine[127, 132]	3.2 (1.1 to 9.0)	6.0 (0.5 to 66.2)	0.5 (0.0 to 7.2)	Medium
Atenolol[95]	Nimodipine[127, 132]	25.2 (1.4 to 467.9)	6.0 (0.5 to 66.2)	4.2 (0.1 to 183.8)	Medium
Flurbiprofen[199]	Nimodipine[127, 132]	5.2 (1.5 to 18.3)	6.0 (0.5 to 66.2)	0.9 (0.1 to 13.0)	Medium
Gabapentin[81, 84, 192]	Nimodipine[127, 132]	2.4 (1.3 to 4.6)	6.0 (0.5 to 66.2)	0.4 (0.0 to 4.8)	Medium
Indomethacin[200]	Nimodipine[127, 132]	1.3 (0.3 to 5.3)	6.0 (0.5 to 66.2)	0.2 (0.0 to 3.5)	Medium
Lisuride[158]	Nimodipine[127, 132]	1.8 (0.9 to 3.5)	6.0 (0.5 to 66.2)	0.3 (0.0 to 3.6)	Medium
Nifedipine[135]	Nimodipine[127, 132]	10.0 (2.9 to 34.2)	6.0 (0.5 to 66.2)	1.7 (0.1 to 24.7)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Rofecoxib[201]	Nimodipine[127, 132]	2.7 (1.1 to 6.5)	6.0 (0.5 to 66.2)	0.4 (0.0 to 5.7)	Medium
Tolfenamic Acid[202]	Nimodipine[127, 132]	11.9 (2.4 to 59.0)	6.0 (0.5 to 66.2)	2.0 (0.1 to 35.5)	Medium
Acebutolol[91]	Rofecoxib[201]	8.9 (1.9 to 42.3)	2.7 (1.1 to 6.5)	3.3 (0.6 to 19.9)	Medium
Amitriptyline[112]	Rofecoxib[201]	3.2 (1.1 to 9.0)	2.7 (1.1 to 6.5)	1.2 (0.3 to 4.6)	Medium
Atenolol[95]	Rofecoxib[201]	25.2 (1.4 to 467.9)	2.7 (1.1 to 6.5)	9.4 (0.4 to 199.1)	Medium
Flurbiprofen[199]	Rofecoxib[201]	5.2 (1.5 to 18.3)	2.7 (1.1 to 6.5)	2.0 (0.4 to 9.1)	Medium
Indomethacin[200]	Rofecoxib[201]	1.3 (0.3 to 5.3)	2.7 (1.1 to 6.5)	0.5 (0.1 to 2.5)	Medium
Lisuride[158]	Rofecoxib[201]	1.8 (0.9 to 3.5)	2.7 (1.1 to 6.5)	0.7 (0.2 to 2.0)	Medium
Nifedipine[135]	Rofecoxib[201]	10.0 (2.9 to 34.2)	2.7 (1.1 to 6.5)	3.7 (0.8 to 17.0)	Medium
Acebutolol[91]	Tolfenamic Acid[202]	8.9 (1.9 to 42.3)	11.9 (2.4 to 59.0)	0.7 (0.1 to 6.9)	Medium
Amitriptyline[112]	Tolfenamic Acid[202]	3.2 (1.1 to 9.0)	11.9 (2.4 to 59.0)	0.3 (0.0 to 1.8)	Medium
Atenolol[95]	Tolfenamic Acid[202]	25.2 (1.4 to 467.9)	11.9 (2.4 to 59.0)	2.1 (0.1 to 59.0)	Medium
Flurbiprofen[199]	Tolfenamic Acid[202]	5.2 (1.5 to 18.3)	11.9 (2.4 to 59.0)	0.4 (0.1 to 3.3)	Medium
Indomethacin[200]	Tolfenamic Acid[202]	1.3 (0.3 to 5.3)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.9)	Medium
Lisuride[158]	Tolfenamic Acid[202]	1.8 (0.9 to 3.5)	11.9 (2.4 to 59.0)	0.1 (0.0 to 0.8)	Medium
Nifedipine[135]	Tolfenamic Acid[202]	10.0 (2.9 to 34.2)	11.9 (2.4 to 59.0)	0.8 (0.1 to 6.3)	Medium
Rofecoxib[201]	Tolfenamic Acid[202]	2.7 (1.1 to 6.5)	11.9 (2.4 to 59.0)	0.2 (0.0 to 1.4)	Medium
Acebutolol[91]	Clonidine[150]	8.9 (1.9 to 42.3)	2.2 (1.0 to 5.2)	4.0 (0.7 to 23.4)	Medium
Amitriptyline[112]	Clonidine[150]	3.2 (1.1 to 9.0)	2.2 (1.0 to 5.2)	1.4 (0.4 to 5.4)	Medium
Atenolol[95]	Clonidine[150]	25.2 (1.4 to 467.9)	2.2 (1.0 to 5.2)	11.3 (0.5 to 235.7)	Medium
Clonidine[150]	Telmisartan[139]	2.2 (1.0 to 5.2)	1.6 (0.7 to 4.0)	1.4 (0.4 to 4.7)	High
Clonidine[150]	Dihydroergotamine[155]	2.2 (1.0 to 5.2)	1.2 (0.8 to 1.8)	1.8 (0.7 to 4.7)	Medium
Clonidine[150]	Fenoprofen[198]	2.2 (1.0 to 5.2)	0.8 (0.3 to 2.2)	2.9 (0.8 to 10.7)	Medium
Clonidine[150]	Lamotrigine[44]	2.2 (1.0 to 5.2)	1.8 (0.8 to 3.7)	1.3 (0.4 to 3.9)	Medium
Clonidine[150]	Lisinopril[136]	2.2 (1.0 to 5.2)	37.7 (2.2 to 649.0)	0.1 (0.0 to 1.2)	Medium
Clonidine[150]	Magnesium[194, 195]	2.2 (1.0 to 5.2)	1.5 (0.6 to 3.4)	1.5 (0.5 to 5.0)	Medium
Clonidine[150]	Montelukast[203]	2.2 (1.0 to 5.2)	1.2 (0.6 to 2.4)	1.9 (0.6 to 5.6)	Medium
Clonidine[150]	Nadolol[98]	2.2 (1.0 to 5.2)	6.0 (0.3 to 118.6)	0.4 (0.0 to 8.4)	Medium
Clonidine[150]	Oxcarbazepine[83]	2.2 (1.0 to 5.2)	0.9 (0.5 to 1.6)	2.6 (0.9 to 7.5)	Medium
Clonidine[150]	Tonabersat[121]	2.2 (1.0 to 5.2)	1.2 (0.6 to 2.4)	1.9 (0.6 to 5.8)	Medium
Clonidine[150]	Flurbiprofen[199]	2.2 (1.0 to 5.2)	5.2 (1.5 to 18.3)	0.4 (0.1 to 1.9)	Medium
Clonidine[150]	Gabapentin[81, 84, 192]	2.2 (1.0 to 5.2)	2.4 (1.3 to 4.6)	0.9 (0.3 to 2.6)	Medium
Clonidine[150]	Indomethacin 4867513	2.2 (1.0 to 5.2)	1.3 (0.3 to 5.3)	1.7 (0.3 to 8.9)	Medium
Clonidine[150]	Lisuride[158]	2.2 (1.0 to 5.2)	1.8 (0.9 to 3.5)	1.3 (0.4 to 3.8)	Medium
Clonidine[150]	Nifedipine[135]	2.2 (1.0 to 5.2)	10.0 (2.9 to 34.2)	0.2 (0.1 to 1.0)	Medium

Appendix Table D84. Clinical response defined as ≥50 percent reduction in monthly migraine frequency or self reported substantial reduction in monthly migraine frequency; indirect adjusted frequentist comparisons of migraine preventive drugs in adults from RCTs (analyzed for drugs that were more effective than placebo) (Strength of indirect evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio (95% CI) with Active Drug vs. Placebo	Odds Ratio (95% CI) with Control Drug vs. Placebo	Odds Ratio (95% CI) with Active vs. Control Drug	Risk of Bias
Clonidine[150]	Nimodipine[127, 132]	2.2 (1.0 to 5.2)	6.0 (0.5 to 66.2)	0.4 (0.0 to 4.7)	Medium
Clonidine[150]	Rofecoxib[201]	2.2 (1.0 to 5.2)	2.7 (1.1 to 6.5)	0.8 (0.2 to 2.8)	Medium
Clonidine[150]	Tolfenamic Acid[202]	2.2 (1.0 to 5.2)	11.9 (2.4 to 59.0)	0.2 (0.0 to 1.1)	Medium

Appendix Table D85. Comparative effectiveness of antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual medium risk of bias randomized controlled clinical trial[204]

Definition of the Outcome	Active Treatment	Control Treatment	Events/ Randomized Rate,% with Active	Events/ Randomized Rate,% with Control	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
>60% reduction in HI in last 4 weeks of treatment phase	**Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)**	**Amitriptyline 100mg/day**	**17/34 22.15**	**34/77 48.65**	**0.5 (0.3 to 0.7)**	**-0.26 (-0.41 to -0.12)**
>60% reduction in HI during the 4-week post-treatment followup phase	Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)	Amitriptyline 100mg/day	17/11 22.15	11/77 15.75	1.4 (0.7 to 2.8)	0.06 (-0.06 to 0.19)
Reduction in HI from baseline during the post-treatment followup period	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	18/17 25.45	17/71 24.35	1.0 (0.6 to 1.9)	0.01 (-0.13 to 0.15)
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	29/34 40.85	34/71 48.65	0.8 (0.6 to 1.2)	-0.08 (-0.24 to 0.09)
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)	Amitriptyline 100mg/day	31/34 40.35	34/77 48.65	0.8 (0.6 to 1.2)	-0.08 (-0.24 to 0.08)
Reduction in HI from baseline during the post-treatment followup period	**Spinal Manipulation (high-velocity, low-amplitude, short-lever arm)**	**Amitriptyline 100mg/day**	**32/17 41.65**	**17/77 24.35**	**1.7 (1.0 to 2.8)**	**0.17 (0.02 to 0.32)**
Reduction in HI (headache index) scores during treatment compared with baseline	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	31/29 40.35	29/77 40.85	1.0 (0.7 to 1.5)	-0.01 (-0.16 to 0.15)
Reduction in HI from baseline during the post-treatment followup period	**Spinal Manipulation**	**Spinal Manipulation + Amitriptyline 100mg/day**	**32/18 41.65**	**18/77 25.45**	**1.6 (1.0 to 2.6)**	**0.16 (0.01 to 0.31)**

HI = headache index ; Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0; CI = confidence interval

Appendix Table D86. Comparative effectiveness of drugs with nonpharmacological treatments for migraine prevention in adults, randomized controlled clinical trials

Reference Country Sample	Drug	Aim	Definition of Migraine	Concurrent Medication	Age % Women Baseline Status of Subjects
Nelson, 1998[204] Country: USA Sample: 218	Amitriptyline	To measure the relative efficacy of amitriptyline, spinal manipulation and the combination of both therapies for the prophylaxis of migraine headache.	International Headache Society criteria	None	Age Mean 37.9 years; % women 78.9 Migraine interfered substantially with work (% of patients): Amitriptyline group: 47.2; SMT group: 41.6; Combined treatment: 46.5 Days with headache (% of possible days during past month):Amitriptyline group: 54.5; SMT group: 53.3; Combined treatment: 50.8 Headache Index (mean diary score (0-70) during the 1-month baseline period): Amitriptyline group: 18.2(9.8); SMT group: 18.2 (9.1); Combined treatment: 10.1 (7.0)
Holroyd, 1995[205] Country: Not reported Sample: 33	Beta-blocker	To evaluate the ability of propranolol to enhance results achieved with relaxation-biofeedback training	International Headache Society diagnostic criteria (Headache Classification Committee of the IHS, 1988)	None	Age Mean 31.7 years; % women 79 Mean years of problem headache: 15.2 years (range, 1-47)
Streng, 2006[206] Country: Germany Sample: 114	Beta-blocker	To investigate whether acupuncture is as effective and safe as metoprolol in the prophylactic treatment migraine under conditions similar to routine care.	International Headache Society criteria	None	Age Mean 40.1 years; % women 87.72 Days with migraine, Mean (SD): Acupuncture: 5.8 (2.5); Metoprolol: 5.8 (2.9) Number of migraine attacks, Mean (SD): Acupuncture: 3.0 (1.4); Metoprolol:2.9 (1.3)
Seng, 2010[207] Country: USA Sample: 232	Beta-blocker	To examine expectancy changes with various combinations of Behavioral Migraine Management and migraine drug therapy	International Classification of Headache Disorders	Rescue drugs such as steroids were allowed	Age Mean 39.1 years; % women 79 Migraine days/30 days, mean (SD): 8.8 (11.5)
Holroyd, 2010[193] Country: USA Sample: 232	Beta-blocker	To determine if the addition of preventive drug treatment (β blocker), brief behavioral migraine management, or their combination improves the outcome of optimized acute treatment in the management of frequent migraine.	International Classification of Headache Disorders	Rescue drugs such as steroids were allowed	Age Mean 38.3 years; % women 79 Mean (SD) migraine days/30 days: Optimized acute treatment + placebo:8.4 (3.5); Optimized acute treatment + β blocker: 8.6 (3.3); Optimized acute treatment plus behavioral migraine management +placebo: 8.1 (3.4); Optimized acute treatment plus behavioral migraine management +β blocker: 8.7 (4.0)

Appendix Table D87. Funding and conflict of interest in randomized controlled clinical trials that examined comparative effectiveness of drugs and nonpharmacological migraine preventive treatments in adults

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Disclosed Relationships
Nelson, 1998[204]	Grant	Yes	Yes	Not reported	Not applicable
Holroyd, 1994[205]	Grant	Not reported	Yes	Not reported	Not applicable
Streng, 2006[206]	Other	Yes	Yes	None	Not applicable
Seng, 2010[207]	Grant	Yes	Yes	Yes	Ms. Seng reports no conflicts of interest. Dr. Holroyd has received support from the National Institutes of Health (NINDS; NS32375), has consulted for ENDO Pharmaceuticals and Takeda Pharmaceuticals North America, and received an investigator initiated grant from ENDO Pharmaceuticals.
Holroyd, 2010[193]	Grant	Yes	Yes	Yes	KA Holroyd has consulted for ENDO Pharmaceuticals and for Takeda Pharmaceuticals North America and received an investigator initiated grant from ENDO Pharmaceuticals. He has also received support from the National Institutes of Health (NINDS; NS32375). CK Cottrell has received research funding and materials from GlaxoSmithKline Pharmaceuticals (GSK) and Merck and participates in industry sponsored research involving GSK, Merck, UCB Pharma, and Allergan. FJ O'Donnell has received research funding and materials from GSK and Merck; receives educational funding from GSK, Merck, and Allergan; participates in industry sponsored research involving GSK, Merck, UCB Pharma, and Allergan; and has consulted for and received honorariums from GSK. GE Corfingley owns stock in Johnson and Johnson, Novartis, and Wyeth Pharmaceuticals.
Wang, 2011[208]	Other	Yes	Yes	None	Not applicable
Dahlof, 1987[209]	Not reported	Not reported	Yes	Not reported	Not applicable

Appendix Table D88. Risk of bias in randomized controlled clinical trials that examined comparative effectiveness of drugs and nonpharmacological migraine preventive treatments in adults

Reference	Masking of the Treatment Status	Masking - Outcome Assessment	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Baseline Similarity	Selective Outcome Reporting	Risk of Bias
Nelson, 1998[204]	Open-label	Not reported	Yes	Unclear	Yes	Frequency: not reported; Severity: not reported; Duration: not reported	Unclear	Medium
Holroyd, 1995[205]	Open-label	Not reported	No	Unclear	Not reported	Not reported	Unclear	High
Streng, 2006[206]	Open-label	Outcome evaluators were blinded	Yes	Clearly Adequate	No (there was a significant difference between the groups for the scale for sensoric pain of the SES)	Frequency: similar; Severity: not reported; Duration: not reported	Unclear	High
Seng, 2010[207]	Double-blind	Not reported	No	Unclear	Yes	Not reported	Unclear	Medium
Holroyd, 2010[193]	Double-blind for the drug and not for behavioral migraine management	Not reported	Yes	Unclear	Not reported The optimized treatment + beta-blocker group had migraine with current frequency for fewer number of years as compared to other groups	Not reported	Unclear	Low
Wang, 2011[208]	Single-blind	The outcome measurements were evaluated by blinded assessors who were unaware of patient allocation	Yes	Clearly adequate	Yes	Not reported	Unclear	Low
Dahlof, 1987[209]	Open-label	The analysis of the diary data was conducted by blind operators who did not know the group of each patient.	No	Unclear	Yes	Frequency: similar Severity: similar; Duration: not reported	Unclear	Medium

Appendix Table D89. Migraine prevention with beta-blockers combined with behavior therapy vs. placebo in adults, results from individual low risk of bias randomized controlled clinical trial[193]

Definition of the Outcome	Active Treatment	Events/ Randomized with Active Treatment	Events/ Randomized with Placebo	Rate of Outcome, % in Active Group [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)**	**53/69**	**8/21**	**76.8[40.0]**	**2.0 (1.2 to 3.5)**	**0.39 (0.16 to 0.62)**
Dropped due to lack of efficacy	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	1/69	2/21	1.4 [7.3]	0.2 (0.0 to 1.6)	-0.08 (-0.21 to 0.05)
Dropped due to side effects	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	6/69	2/21	8.7 [9.1]	0.9 (0.2 to 4.2)	-0.01 (-0.15 to 0.13)
Dropped out	Behavioral migraine management and relaxation + propranolol (max dose 240mg/day) or nadolol (max dose 120mg/day)	24/69	9/21	34.8 [41.8]	0.8 (0.4 to 1.5)	-0.08 (-0.32 to 0.16)

Bold = significant differences at 95% confidence limit when 95%CI of absolute risk difference do not include 0
CI = confidence interval

Appendix Table D90. Strength of evidence - efficacy 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) vs. placebo for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[193]

Definition of the Outcome	Active Treatment	Control Treatment	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Placebo	Propranolol/nadolol	Low	Yes	NA	No	Low
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	Low	Yes	NA	No	Low
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	Low	Yes	NA	No	Low

Appendix Table D91. Efficacy 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) vs. placebo for migraine prevention in adults, results from individual medium risk of bias randomized controlled clinical trial[207]

Definition of the Outcome	Active Treatment	Randomized for Active Treatment [Placebo]	Mean [Standard Deviation] with Active Treatment	Mean [Standard Deviation] with Placebo	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Mean HSE (Headache Management Self-Efficacy Scale) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**144.8 [23.6]**	**117.2 [18.6]**	**27.6 (20.2 to 35.0)**	**1.3 (0.9 to 1.7)**
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**63.9 [7.7]**	**55.5 [9.5]**	**8.4 (5.3 to 11.5)**	**1.0 (0.6 to 1.4)**
Mean Chance HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**21.1 [8.4]**	**30.7 [8.5]**	**-9.6 (-12.6 to -6.6)**	**-1.1 (-1.5 to -0.8)**
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	**Propranolol(240mg/day) or nadolol (120mg/day) plus behavioral Migraine Management**	**69 [55]**	**31.6 [6.9]**	**35.4 [6.5]**	**-3.8 (-6.2 to -1.4)**	**-0.6 (-0.9 to -0.2)**

Bold = significant differences at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D92. Comparative effectiveness of antidepressant amitriptyline, 100mg/day and spinal manipulation on intermediate outcomes in adults with migraine, individual medium risk of bias randomized controlled clinical trial[204]

Definition of the Outcome	Active Treatment	Control Treatment	Mean [Standard Deviation] with Active Treatment	Mean [Standard Deviation] with Drug	Mean Difference (95% CI)	Standardized Cohen Mean Difference (95% CI)
HI (Headache Index): mean of last 4 week of the treatment period	Spinal Manipulation The spinal manipulation administered was a type described as high-velocity, low-amplitude, and short-lever arm.	Amitriptyline 100mg/days	9.8 [6.3]	9.1 [6.3]	0.7 (-1.3 to 2.7)	0.1 (-0.2 to 0.4)
HI (Headache Index): mean of last 4 week of the treatment period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	9.8 [6.3]	9.1 [6.3]	0.7 (-1.4 to 2.8)	0.1 (-0.2 to 0.4)
HI (Headache Index): mean during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	12.6 [7.0]	12.6 [7.0]	0.0 (-2.3 to 2.3)	0.0 (-0.3 to 0.3)
HI (Headache Index): mean during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	12.6 [7.0]	12.6 [7.0]	0.0 (-2.3 to 2.3)	0.0 (-0.3 to 0.3)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation	Amitriptyline 100mg/days	1.1 [1.1]	0.9 [1.0]	0.2 (-0.1 to 0.5)	0.2 (-0.1 to 0.5)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	1.1 [1.1]	0.9 [1.0]	0.2 (-0.1 to 0.5)	0.2 (-0.1 to 0.5)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	1.1 [1.3]	1.4 [1.3]	-0.3 (-0.7 to 0.1)	-0.2 (-0.6 to 0.1)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day		1.2 [1.5]	1.4 [1.3]	-0.2 (-0.7 to 0.3)	-0.1 (-0.5 to 0.2)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation	Amitriptyline 100mg/days	73.6 [10.7]	71.2 [10.5]	2.4 (-1.0 to 5.8)	0.2 (-0.1 to 0.6)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/days	72.9 [10.5]	71.2 [10.5]	1.7 (-1.8 to 5.2)	0.2 (-0.2 to 0.5)

Appendix Table 92. Comparative effectiveness of antidepressant amitriptyline, 100mg/day and spinal manipulation on intermediate outcomes in adults with migraine, individual medium risk of bias randomized controlled clinical trial (continued)

Definition of the Outcome	Active Treatment	Control Treatment	Mean [Standard Deviation] with Active Treatment	Mean [Standard Deviation] with Drug	Mean Difference (95% CI)	Standardized Cohen Mean Difference (95% CI)
HI (Headache Index) : mean of last 4 week of the treatment period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	9.8 [6.3]	9.8 [6.3]	0.0 (-2.0 to 2.0)	0.0 (-0.3 to 0.3)
HI (Headache Index) : mean during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	9.8 [7.0]	12.6 [7.0]	-2.8 (-5.1 to -0.5)	-0.4 (-0.7 to -0.1)
OTC pills/day: mean of last 4 weeks of the treatment period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	1.1 [1.1]	1.1 [1.1]	0.0 (-0.4 to 0.4)	0.0 (-0.3 to 0.3)
OTC pills/day: mean during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	1.1 [1.3]	1.2 [1.5]	-0.1 (-0.6 to 0.4)	-0.1 (-0.4 to 0.3)
General health status (S-36): % points during post-treatment follow-up period	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	73.6 [10.7]	72.9 [10.5]	0.7 (-2.7 to 4.1)	0.1 (-0.3 to 0.4)

OTC = over-the-counter medications

Appendix Table D93. Dose response in acute treatment utilization with onabotulinumtoxin A for migraine prevention in adults (individual low risk of bias RCT)[11]

Outcome	Dose of Onabotulinumtoxin A in Active vs. Control, units	Events/Randomized with Larger Dose	Events/Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Patients using and overusing acute headache pain medications	225 vs. 150	144/182	152/168	0.9 (0.8 to 1.0)	**-0.11 (-0.19 to -0.04)**
Patients using and overusing acute headache pain medications	225 vs. 150	151/182	157/168	0.9 (0.8 to 1.0)	**-0.10 (-0.17 to -0.04)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D94. Dose response in global assessment of treatment success with onabotulinumtoxin A for migraine prevention in adults (individual low risk of bias RCT)[8]

Outcome	Dose of Onabotulinumtoxin A in Active vs. Control, Units	Events/Randomized with Larger Dose	Events/Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Improvement in global assessment (patient score) week 4-8	240 vs. 120	11/43	14/43	0.8 (0.4 to 1.5)	-0.07 (-0.26 to 0.12)
Improvement in global assessment (investigator score) week 4-8	240 vs. 120	12/43	11/43	1.1 (0.5 to 2.2)	0.02 (-0.16 to 0.21)
Improvement in global assessment (patient score) week 4-12	240 vs. 120	16/43	16/43	1.0 (0.6 to 1.7)	0.00 (-0.20 to 0.20)
Improvement in global assessment (investigator score) week 4-12	240 vs. 120	17/43	18/43	0.9 (0.6 to 1.6)	-0.02 (-0.23 to 0.18)

CI = confidence interval

Appendix Table D95. Dose response reduction in migraine attacks by≥ 50% from baseline with topiramate in adults

Reference	Active Dose	Control Dose	Relative Risk (95% CI)	Weight	Absolute Risk Difference (95% CI)	Weight
Brandes, 2004[22]	100mg/day	50mg/day	1.3 (0.9 to 1.7)	33.7	0.10 (-0.02 to 0.23)	32.30
Silberstein, 2003[21]	100mg/day	50mg/day	1.5 (1.1 to 2.1)	31.9	0.19 (0.07 to 0.31)	33.27
Silberstein, 2004[23]	100mg/day	50mg/day	1.5 (1.1 to 2.0)	34.5	0.18 (0.06 to 0.30)	34.43
Pooled, random effects model, inverse variance	**100mg/day**	**50mg/day**	**1.4 (1.2 to 1.7)**	**100.0**	**0.16 (0.09 to 0.23)**	**100**
Heterogeneity			P value = 0.6 I squared = 0%		P value = 0.6 I squared = 0%	
Brandes, 2004[22]	200mg/day	100mg/day	1.0 (0.7 to 1.2)	29.42	-0.02 (-0.15 to 0.11)	33.49
Silberstein, 2003[21]	200mg/day	100mg/day	1.0 (0.8 to 1.2)	34.63	-0.02 (-0.15 to 0.11)	32.75
Silberstein, 2004[23]	200mg/day	100mg/day	1.0 (0.8 to 1.2)	35.95	-0.02 (-0.14 to 0.11)	33.77
Pooled, random effects model, inverse variance	**200mg/day**	**100mg/day**	**1.0 (0.8 to 1.1)**	**100**	**-0.02 (-0.09 to 0.05)**	**100**
Heterogeneity			P value = 0.0 I squared = 0%		P value = 0.0 I squared = 0%	
Brandes, 2004[22]	200mg/day	50mg/day	1.2 (0.9 to 1.6)	34.17	0.08 (-0.05 to 0.20)	33.49
Silberstein, 2003[21]	200mg/day	50mg/day	1.5 (1.1 to 2.0)	31.43	0.17 (0.04 to 0.29)	32.44
Silberstein, 2004[23]	200mg/day	50mg/day	1.4 (1.1 to 1.9)	34.4	0.16 (0.04 to 0.29)	34.07
Pooled, random effects model, inverse variance	**200mg/day**	**50mg/day**	**1.4 (1.2 to 1.6)**	**100**	**0.14 (0.06 to 0.21)**	**100**
Heterogeneity			P value = 0.6 I squared = 0%		P value = 0.6 I squared = 0%	

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D96. Dose response migraine prevention with divalproex in adults, results from low risk of bias randomized controlled clinical trial[47]

Outcome	Daily Doses of Divalproex	Events/ Randomized with Larger Dose	Events/ Randomized with Smaller Dose	Relative Risk	Absolute Risk Difference (95% CI)	Attributable Events per 1000 Treated (95% CI)
50% improvement in migraine attacks impairing usual activities	**1000 mg vs. 500 mg**	**16/43**	**26/45**	**0.6 (0.4 to 1.0)**	**-0.21 (-0.41 to 0.00)**	**-206 (-410 to -1)**
50% improvement in migraine attacks impairing usual activities	1500 mg vs. 500 mg	24/44	26/45	0.9 (0.7 to 1.4)	-0.03 (-0.24 to 0.17)	NS
50% improvement in migraine attacks impairing usual activities	1500 mg vs. 1000 mg	24/44	16/43	1.5 (0.9 to 2.4)	0.17 (-0.03 to 0.38)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1000 mg vs. 500 mg	16/43	19/45	0.9 (0.5 to 1.5)	-0.05 (-0.25 to 0.15)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg vs. 500 mg	19/44	19/45	1.0 (0.6 to 1.7)	0.01 (-0.20 to 0.22)	NS
50% improvement in migraine attacks necessitating symptomatic medication	1500 mg vs. 1000 mg	19/44	16/43	1.2 (0.7 to 1.9)	0.06 (-0.15 to 0.27)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1000 mg vs. 500 mg	18/43	21/45	0.9 (0.6 to 1.4)	-0.05 (-0.26 to 0.16)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1500 mg vs. 500 mg	22/44	21/45	1.1 (0.7 to 1.6)	0.03 (-0.17 to 0.24)	NS
50% improvement in migraine attacks with nausea, vomiting, phonophobia or photophobia	1500 mg vs. 1000 mg	22/44	18/43	1.2 (0.8 to 1.9)	0.08 (-0.13 to 0.29)	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level; NS = not significant

Appendix Table D97. Migraine management programs examined in randomized controlled clinical trials

Reference Country Sample	Aim	Definition of Migraine	Concurrent Medication	Age of Subjects (Mean or Median) % Women Baseline Migraine Severity
Lemstra, 2002[210] Country: Not reported Sample: 80	To test the effectiveness of a multidisciplinary management program for migraine treatment in a group, low-cost, nonclinical setting	International Headache Society criteria	Not reported	Mean 34.5 years 66.3% women Average pain in last month (1-10): Intervention: 7.34±1.87, Control: 7.14±2.02 Pain Disability Index: Intervention: 32.95±12.92, Control: 34.19±16.06
Matchar, 2008[211] Country: USA Sample: 614	To determine of patients cared for in a coordinated headache management program would achieve reduced headache disability compared with patients in usual care	Not reported	Not reported	Mean 43.5 years 87% women Migraine Disability Assessment (MIDAS), mean (SD): 48.8 (64.0)
Rothrock, 2006[212] Country: USA Sample: 100	To determine whether the addition of patient education to routine medical management improves the clinical status of migraine patients and reduces their utilization of healthcare resources.	International Headache Society criteria	Prophylactic medication was prescribed to all "school" patients and to 41 (82%) of the "no school" patients: antiepileptic drug or gabapentin.	Mean 42.5 years 92% women Mean headache days: intervention=14, control=23
Fritsche, 2010[213] Country: Germany Sample: 158	To compare the therapeutic effect of a cognitive-behavioral minimal contact program (MCT) to the effect of a brochure (bibliotherapy) for the prevention of medication overuse headache (MOH) in migraine patients.	International Headache Society criteria -II criteria	Not reported	Mean 48 years 91% women Migraine days, mean (SD):MCT=7.23 (3.70), bibliography=7.27 (3.82); Headache disability, mean (SD): MCT=4.46 (1.80), bibliography=4.16 (1.56)
Sondergaard, 2006[214] Country: Denmark Sample: 2463	To evaluate the impact of an intensive pharmaceutical care campaign targeting inappropriate use of triptans	Not reported	Triptans	Median: Intervention: 47 years, Control: 46 years 83% women Baseline severity not reported
Hoffmann, 2008[215] Country: Germany Sample: 410	To evaluate the effects of pharmaceutical care (defined as intensified structured counseling between patient and pharmacist, including the use of drug databases), for patients with headache or migraine, on both clinical and psychological endpoints.	Criteria of the International Headache Society and the Kiel Headache Questionnaire	Not reported	Mean 43,3 years 83% women Headache attacks/month, n: Intervention group: 5.12±7.29, Control group: 4.81±5.65 Treated: Intervention group: 27.43±70.27, Control group: 22.37±56.87 Intensity of headache pain: Untreated: Intervention group: 8.38±1.52, Control group: 8.45±1.61

Appendix Table D98. Funding and conflict of interest in randomized controlled clinical trials that examined migraine management programs in adults

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Disclosed Relationships
Lemstra, 2002[210]	Not reported	Yes	Yes	Not reported	Not applicable
Matchar, 2008[211]	Grant	Yes	Yes	Yes	Richard Lipton has consulted for, conducted studies funded by, and/or received lecture honoraria from Advanced Bionics, Allergan, AstraZeneca, Boehringer-Ingelheim, Bristol-Myers Squibb, Cierra, Endo, GlaxoSmithKline, Merck, Neualieve, Ortho-McNeil, Pfizer, Pozen, ProEthics and St Judes. The following authors have no conflict of interest. Including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript: David B. Matchar, Gregory Samsa, Annette Jurgelski. Dr. Harpole and Kori are presently employees of GlaxoSmithKline.
Rothrock, 2006[212]	Not reported	Yes	Yes	Not reported	Not applicable
Fritsche, 2010[213]	Grant	Yes	Yes	None	Not applicable
Sondergaard, 2006[214]	Grant	Yes	Not reported	Not reported	Not applicable
Hoffmann, 2008[215]	Industry + Other	Yes	Yes	Not reported	Not reported, however, Michael Cramer is the Head of Division for Pharmacies and Health Provision, Ministry for Work, Social, Health, Family and Gender Issues, Mainz, Germany. Doris Gresselmeyer is a pharmacist from Linden - Apotheke, Bremen, Germany

Appendix Table D99. Risk of bias in randomized controlled clinical trials that examined migraine management programs in adults

Reference	Masking of the Treatment Status	Masking - Outcome Assessment	Intention to Treat Analysis Preplanned	Allocation Concealment	Adequacy of Randomization	Groups Similarity	Risk of Bias
Lemstra, 2002[210]	Open-label (Therapists were blind as to which specific outcome variables were primarily under evaluation).	The outcome assessor was blind to the intervention status.	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: not reported	Medium
Matchar, 2008[211]	Not reported	Yes	No	Unclear	Not adequate	Frequency: not reported; Severity: similar (MIDAS score include headache days and severity of pain and they were similar across the groups); Duration: not reported	Medium
Rothrock, 2006[212]	Not reported	Yes	No	Unclear	Not adequate : difference in episodic migraine in control group (36% vs. 2%); frequent episodic migraine (72% vs. 28%); and mean Migraine Disability Assessment (MIDAS) score was lower in the intervention group	Not reported	Medium
Fritsche, 2010[213]	Not reported	Not reported	No	Clearly adequate (central randomization)	Not reported (There were no patients with aura in the control group)	Frequency: similar; Severity: similar; Duration: not reported	Low
Sondergaard, 2006[214]	Not reported	Not reported	Not reported	Unclear	Yes	Not reported	Low
Hoffman, 2008[215]	Not reported	Not reported	Yes	Unclear	Yes	Frequency: similar; Severity: similar; Duration: similar	Low

Appendix Table D100. Description of disease management programs for migraine prevention in adults

Reference	Program	Description	Control	Description
Lemstra, 2002[210]	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 discharge. The initial neurologist evaluation was intended to confirm the diagnosis, obtain a detailed history, and confirm appropriateness to participate. The physical therapist provided a detailed biomechanical evaluation, provided education on hurt versus harm, identified barriers to participation, and initiated an action plan to prevent dropout. The exercise therapist supervised the exercise therapy sessions, which included submaximal aerobic exercise, stretching, and light weight training, and monitored attendance and created a social no intimidating environment for the patients. The psychologist provided 1 group lecture on relaxation training and another on behavioral modification and stress management. The dietitian provided 1 group lecture on general dietary goals and explained how to substitute alternatives to potential dietary triggers. The massage therapist provided 2 individual sessions with the goal of relaxation and a means of reward after initial exercise sessions rather than any type of therapeutic benefit.	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 discharge. The initial neurologist evaluation was intended to confirm the diagnosis, obtain a detailed history, and confirm appropriateness to participate. The physical therapist provided a detailed biomechanical evaluation, provided education on hurt versus harm, identified barriers to participation, and initiated an action plan to prevent dropout. The exercise therapist supervised the exercise therapy sessions, which included submaximal aerobic exercise, stretching, and light weight training, and monitored attendance and created a social no intimidating environment for the patients. The psychologist provided 1 group lecture on relaxation training and another on behavioral modification and stress management. The dietitian provided 1 group lecture on general dietary goals and explained how to substitute alternatives to potential dietary triggers. The massage therapist provided 2 individual sessions with the goal of relaxation and a means of reward after initial exercise sessions rather than any type of therapeutic benefit.	Standard medical care with the patient's family physician	Standard medical care with the patient's family physician

Appendix Table 100. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
Matchar, 2008[211]	Headache management program: This involved developing a set of general functional specifications for a headache program, identifying local site-specific barriers to implementing the functional specifications, and working with investigators to develop a set of mutually acceptable tools that assured comparability and standardization across sites. The intervention was administered by a mid-level provider (e.g. nurse practitioner or PA) with expertise in headache evaluation and management. The program included an educational session attended by all intervention patients either individually or as a group (the headache class). Patients were given educational materials that included information on headache types and etiologies, pharmacologic treatment, triggers, sleep hygiene, and relaxation techniques.	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. It also included an educational session attended by all intervention patients either individually or as a group; an initial visit to the clinic for evaluation; and follow-up visits (in-person or by telephone) at 1, 3, and 6 months.	Usual care	Continue with current clinician and no access to the headache management program
Fritsche, 2010[213]	Cognitive-behavioral minimal contact program (MCT)	It consisted of 5 sessions with sic participants and lasting 2 hours (2*50min plus 20-min plus a 20-min break) each. The first unit (session) was called "Introduction and syndrome education". It main components included information about symptoms, pathophysiology and pathopsychology of migraine as well as instructions for progressive muscle relaxation (PMR). The 2nd unit was called "Medication rules and the risk of Medication Overuse Headache" including information about acute and prophylactic migraine medication and medication overuse headache-symptoms and patho-mechanisms. The 3rd unit was called "Medication intake behavior" aimed at raising awareness for "external" (e.g. availability of drugs, stock-keeping, iatrogenic risk factors like doctor shopping) and "internal" (e.g. fear of attack and losing social functioning, stress level in private and professional life) influences on patient's medication intake behavior. The 4th	Brochure (bibliography)	The participants received two brochures: a detailed brochure as a patient guide with information about physiological and psychological aspects of migraine, medication-overuse headache and migraine medication. It summarized the topics which were covered by the MCT, written in the style of a self-help manual containing instructions for exercises to minimize drug consumption and instructions for PMR. Each chapter of the brochure ended with questions about the

Appendix Table 100. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
		unit was called "general and personal risk factors for drug intake" and established a general risk profile of medication overuse for each patient. The 5th unit was called "everyday transfer" with the aim of establishing individual goals for future drug intake and learning how to make use of social support to control intake behavior. At the end of the 5th session, participants received the brochures given to the biblio-group.		content of the chapter which the patients were to answer. The brochure was called ‘‘Migraine and medication – Which problems can arise and what to do”. The second brochure (extended information about migraine medication) contained information material without any exercise instructions. Part one of the brochure described the indication, the pharmacological mechanisms of action and the side-effects of different acute migraine medications, and part two discussed prophylactic medication. There was no face-to-face contact and the participants had the opportunity to obtain advice by telephone if they had any questions regarding the brochures.
Rothrock, 2006[212]	Standardized course of didactic instructions regarding migraine biogenesis and management ("headache school")	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 1 of the neurology investigators (Johns Rothrock).The 3 “headache school” classes primarily involved the topics of migraine biogenesis, acute treatment of migraine, and prevention of migraine. Working together, in each class 2 instructors provided 30 to 45 minutes of didactic instruction, followed by a review of hard copy materials related to the primary topic and permanently provided to the participants, demonstration of therapeutic devices (e.g., the autoinjector used to administer sumatriptan; subcutaneous administration of Dihydroergotamine via a 1 cc syringe and 27 g needle), and, to close, an interactive question and answer session cum open forum. All individuals serving as patient instructors underwent 12 hours of classroom instruction in headache theory and treatment, received and reviewed a	Routine medical management	

Appendix Table 100. Description of disease management programs for migraine prevention in adults (continued)

Reference	Program	Description	Control	Description
		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.		
Hoffmann, 2008[215]	Pharmaceutical care for migraine	Pharmacists from the intervention pharmacies participated in a 2-day central training program conducted by a physician and a pharmacist who were employees of the university. 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 that was distributed to the intervention pharmacists upon completion of the program. The manual was developed by the Federal Union of German Associations of Pharmacists, in cooperation with the principal investigators, and contains central definitions of pharmaceutical care (PC),with a focus on PC in patients with different types of pain (e.g., headache, muscle).	Standard counseling	Patients received the regular pharmaceutical consultation; their pharmacists were not specially trained, did not receive the standard manual, and were not included in the documentation scheme for counseling. This regular counseling includes general information about application and possible adverse drug effects.
Sondergaard, 2006[214]	Intensive pharmaceutical care campaign	Pharmacists from the intervention pharmacies provided the intervention. They were encouraged to involve the pharmacy assistants. A manual given to pharmacy staff described how to identify inappropriate triptan use, how to establish a dialogue and how to ask questions. Moreover, it offered suggestions for relevant questions, advice, literature on headache, migraine and pharmaceutical care, and included a checklist. The training package was developed in cooperation with the Danish College of Pharmacy Practice (Pharmakon). When presenting a triptan prescription at the pharmacy, the user received a folder designed to support the dialogue and assist the pharmacist in detecting triptan overuse. It included information on the campaign and questions on the patient's drug use, e.g. the type of headache for which the patient used triptans, monthly consumption of triptans, repeated use of triptans even if the first dose had no effect on the attack, and the frequency of use of other types of painkillers. The dialogue between the pharmacist and the patient took place immediately after the folder had been read and its questions answered. To ensure an undisturbed, confidential conversation, the pharmacies were encouraged to let the dialogue with triptan users take place in a separate room. Each dialogue was estimated to last on average 15 minutes and each triptan user participated only once.	Control pharmacy	

Appendix Table D101. Adherence to multidisciplinary intervention for migraine prevention in adults compared to standard care, results from medium risk of bias randomized controlled clinical trial[210]

Definition of the Outcome	Events/Randomized with Multidisciplinary Intervention	Events/Randomized with Usual Care	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Quit intervention due to inefficiency	1/44	0/36	2.5 (0.1 to 58.8)	0.02 (-0.04 to 0.09)
Quit intervention	3/44	0/36	5.8 (0.3 to 107.9)	0.07 (-0.02 to 0.15)

CI = confidence interval

Appendix Table D102. Effectiveness of multidisciplinary intervention for migraine prevention in adults compared to standard care (results from medium risk of bias randomized controlled clinical trial)[210]

Definition of the Outcome at 3 Months of followup After the Intervention	Mean [Standard Deviation] with Multidisciplinary Intervention	Mean [Standard Deviation] with Usual Care	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
% change in self-perceived pain frequency (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**56.9 [9.1]**	**-2.2 [2.2]**	**59.15 (56.36 to 61.94)**	**8.5 (7.1 to 9.9)**
% change in pain intensity (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**38.2 [8.5]**	**-2.8 [2.0]**	**40.96 (38.36 to 43.56)**	**6.3 (5.2 to 7.4)**
% change in pain duration (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**47.2 [8.3]**	**-5.0 [2.9]**	**52.16 (49.52 to 54.80)**	**8.0 (6.7 to 9.4)**
% change in functional status (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**51.6 [7.7]**	**-0.6 [2.0]**	**52.15 (49.78 to 54.52)**	**8.9 (7.4 to 10.3)**
% change in quality of life (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**57.1 [8.2]**	**-1.9 [1.9]**	**58.99 (56.49 to 61.49)**	**9.5 (8.0 to 11.1)**
% change in Pain Disability Index (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**18.8 [2.2]**	**1.7 [1.0]**	**17.08 (16.35 to 17.81)**	**9.6 (8.0 to 11.2)**
% change in Beck Depression Inventory (Visual Analogue Scale that included values from 100% worse to 100% improvement)	**10.6 [1.3]**	**1.2 [0.5]**	**9.44 (9.04 to 9.84)**	**9.7 (8.1 to 11.2)**

Bold = significant differences at 95% CI when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D103. Reduction in disability with headache management program for migraine prevention in adults compared to standard care (results from medium risk of bias randomized controlled clinical trial)[211]

Definition of the Outcome	Events/Randomized with Headache Management Program	Events/Randomized with Usual Care	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1000 Treated (95% CI)
6 months: Achieved a Migraine Disability Assessment (MIDAS) score of 0 reflecting no headache-related disability	**124/305**	**65/309**	**1.9 (1.5to 2.5)**	**0.20 (0.12 to 0.27)**	**5 (4 to 8)**	**196 (125 to 258)**

CI = confidence interval

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D104. Effectiveness of headache management program for migraine prevention in adults compared to standard care (results from medium risk of bias randomized controlled clinical trial)[211]

Definition of the Outcome	Mean [Standard Deviation] with Headache Management Program	Mean [Standard Deviation] with Usual Care	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
MIDAS score at 6 months	**15.9 [24.4]**	**23.6 [37.6]**	**-7.70 (-12.71 to -2.69)**	**-0.2 (-0.4 to -0.1)**
Quality of life (SF-36): Physical function domain	**84.0 [20.6]**	**79.0 [22.3]**	**5.00 (1.60 to 8.40)**	**0.2 (0.1 to 0.4)**
Quality of life (SF-36): Role physical domain	**75.7 [24.8]**	**67.5 [25.1]**	**8.20 (4.25 to 12.15)**	**0.3 (0.2 to 0.5)**
Quality of life (SF-36): Pain domain	**63.8 [23.0]**	**55.5 [22.5]**	**8.30 (4.70 to 11.90)**	**0.4 (0.2 to 0.5)**
Quality of life (SF-36): General health domain	53.3 [9.9]	52.3 [9.8]	1.00 (-0.56 to 2.56)	0.1 (-0.1 to 0.3)
Quality of life (SF-36): Vitality domain	**52.8 [21.4]**	**48.8 [19.3]**	**4.00 (0.78 to 7.22)**	**0.2 (0.0 to 0.4)**
Quality of life (SF-36): Social function domain	**73.4 [24.9]**	**68.7 [24.8]**	**4.70 (0.77 to 8.63)**	**0.2 (0.0 to 0.3)**
Quality of life (SF-36): Role emotional domain	**77.9 [24.1]**	**73.8 [25.6]**	**4.10 (0.17 to 8.03)**	**0.2 (0.0 to 0.3)**
Quality of life (SF-36): Mental health domain	69.7 [19.2]	66.8 [19.9]	2.90 (-0.19 to 5.99)	0.1 (0.0 to 0.3)
Quality of life (SF-36): Physical summary domain	**47.6 [7.7]**	**45.0 [8.4]**	**2.60 (1.33 to 3.87)**	**0.3 (0.2 to 0.5)**
Quality of life (SF-36): Mental summary domain	45.4 [11.6]	43.9 [11.6]	1.50 (-0.34 to 3.34)	0.1 (0.0 to 0.3)
General health (from 1[excellent] to 5 [poor])	**2.4 [0.9]**	**2.7 [0.9]**	**-0.30 (-0.44 to -0.16)**	**-0.3 (-0.5 to -0.2)**
Change since last year (from 1 [much better] to 5 [much worse])	**2.5 [0.9]**	**2.8 [0.9]**	**-0.30 (-0.44 to -0.16)**	**-0.3 (-0.5 to -0.2)**
Depression (PHQ-9) (Patient Health Questionnaire-Short Form)	**5.6 [5.2]**	**6.6 [5.3]**	**-1.00 (-1.83 to -0.17)**	**-0.2 (-0.3 to 0.0)**
MIDAS: Missed work days	1.2 [2.7]	1.6 [6.5]	-0.40 (-1.19 to 0.39)	-0.1 (-0.2 to 0.1)
MIDAS: Missed half work days	3.9 [7.9]	5.2 [8.8]	-1.30 (-2.62 to 0.02)	-0.2 (-0.3 to 0.0)
MIDAS: Missed house days	**5.0 [10.2]**	**7.1 [11.2]**	**-2.10 (-3.79 to -0.41)**	**-0.2 (-0.4 to 0.0)**
MIDAS: Missed half house days	**3.9 [6.0]**	**6.8 [10.5]**	**-2.90 (-4.25 to -1.55)**	**-0.3 (-0.5 to -0.2)**
MIDAS: Missed family days	**2.4 [4.9]**	**3.6 [8.1]**	**-1.20 (-2.26 to -0.14)**	**-0.2 (-0.3 to 0.0)**
MIDAS: Headache days	**13.8 [17.6]**	**17.7 [20.9]**	**-3.90 (-6.95 to -0.85)**	**-0.2 (-0.4 to 0.0)**
MIDAS: Headache pain (from 0 [no pain at all] to 10 [pain as bad as it can be])	**5.6 [2.3]**	**6.1 [2.2]**	**-0.50 (-0.86 to -0.14)**	**-0.2 (-0.4 to -0.1)**
Worried about headache (from 0 [not worried at all] to 10 [extremely worried])	**4.4 [2.7]**	**5.1 [2.7]**	**-0.70 (-1.13 to -0.27)**	**-0.3 (-0.4 to -0.1)**
Problems with headache management (from 1 [no problems] to 4 [severe amount of problems])	**2.1 [0.8]**	**2.4 [0.7]**	**-0.30 (-0.42 to -0.18)**	**-0.4 (-0.6 to -0.2)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Headache care	**1.8 [1.0]**	**2.4 [1.2]**	**-0.60 (-0.77 to -0.43)**	**-0.5 (-0.7 to -0.4)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Understanding	**1.7 [1.0]**	**2.4 [1.2]**	**-0.70 (-0.87 to -0.53)**	**-0.6 (-0.8 to -0.5)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Medications	**2.0 [1.1]**	**2.5 [1.2]**	**-0.50 (-0.68 to -0.32)**	**-0.4 (-0.6 to -0.3)**
Satisfaction with care (from 1 [very satisfied] to 5 [very dissatisfied]): Medical care in general	**1.7 [0.9]**	**2.0 [1.0]**	**-0.30 (-0.45 to -0.15)**	**-0.3 (-0.5 to -0.2)**

Bold = significant differences at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D105. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from medium risk of bias randomized controlled clinical trial)[216]

Definition of the Outcome	Mean [Standard Deviation] with Cognitive-behavioral Minimal Contact Program	Mean [Standard Deviation] with Educational Brochure	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Headache days: 3 months after treatment	8.6 [5.5]	8.1 [4.8]	0.44 (-1.21 to 2.09)	0.1 (-0.2 to 0.4)
Headache days: 1-2 years after treatment	8.7 [5.3]	8.3 [5.2]	0.35 (-1.32 to 2.02)	0.1 (-0.3 to 0.4)
Migraine days: 3 months after treatment	6.2 [4.0]	5.5 [3.2]	0.70 (-0.44 to 1.84)	0.2 (-0.1 to 0.5)
Migraine days: 1-2 years after treatment	6.2 [4.0]	5.8 [3.8]	0.31 (-0.94 to 1.56)	0.1 (-0.2 to 0.4)
Headache disability: 3 months after treatment	4.6 [2.0]	4.3 [1.9]	0.36 (-0.26 to 0.98)	0.2 (-0.1 to 0.5)
Headache disability: 1-2 years after treatment	4.4 [2.2]	4.4 [1.7]	-0.01 (-0.63 to 0.61)	0.0 (-0.3 to 0.3)
Intake at headache days: 3 months after treatment	5.9 [3.2]	6.5 [3.2]	-0.54 (-1.57 to 0.49)	-0.2 (-0.5 to 0.2)
Intake at headache days: 1-2 years after treatment	6.2 [3.7]	6.0 [2.8]	0.18 (-0.86 to 1.22)	0.1 (-0.3 to 0.4)
Intake at migraine days: 3 months after treatment	4.8 [3.0]	4.8 [2.8]	0.08 (-0.85 to 1.01)	0.0 (-0.3 to 0.3)
Intake at migraine days: 1-2 years after treatment	5.0 [3.5]	5.0 [2.8]	0.01 (-1.00 to 1.02)	0.0 (-0.3 to 0.3)
CPAQ-AE ('Activity engagement' subscale of the "Chronic Pain Acceptance Questionnaire"): 3 months after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	34.6 [10.9]	34.9 [9.4]	-0.32 (-3.56 to 2.92)	0.0 (-0.4 to 0.3)
CPAQ-AE ('Activity engagement' subscale of the "Chronic Pain Acceptance Questionnaire"): 1-2 years after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	35.5 [10.8]	34.4 [9.4]	1.12 (-2.11 to 4.35)	0.1 (-0.2 to 0.4)
CPAQ-PW ('Pain willingness' subscale of the "Chronic Pain Acceptance Questionnaire"): 3 months after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	22.5 [8.9]	23.4 [8.0]	-0.89 (-3.58 to 1.80)	-0.1 (-0.4 to 0.2)
CPAQ-PW ('Pain Willingness' subscale of the "Chronic Pain Acceptance Questionnaire"): 1-2 years after intervention; lower score indicates worse and higher score indicates better ability to maintain functioning in the presence of chronic pain	26.8 [9.6]	25.2 [7.6]	1.55 (-1.21 to 4.31)	0.2 (-0.1 to 0.5)
FSS-CATA ('Catastrophising cognitions' subscale of the "Pain-related self instructions" questionnaire): 3 months after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	24.2 [7.3]	25.5 [7.3]	-1.33 (-3.67 to 1.01)	-0.2 (-0.5 to 0.1)
FSS-CATA ('Catastrophising cognitions' subscale of the "Pain-related self instructions" questionnaire): 1-2 years after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	21.4 [10.3]	22.1 [8.5]	-0.68 (-3.70 to 2.34)	-0.1 (-0.4 to 0.2)

Appendix Table 105. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from medium risk of bias randomized controlled clinical trial) (continued)

Definition of the Outcome	Mean [Standard Deviation] with Cognitive-behavioral Minimal Contact Program	Mean [Standard Deviation] with Educational Brochure	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
FSS-FUNC ('Functional cognitions' subscale of the "Pain-related self instructions" questionnaire): 3 months after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	**34.2 [14.7]**	**29.8 [6.1]**	**4.32 (0.79 to 7.85)**	**0.4 (0.1 to 0.7)**
FSS-FUNC ('Functional cognitions' subscale of the "Pain-related self instructions" questionnaire): 1-2 years after intervention. It consists of 9 items on a 6-point scale (0=almost never, 5=almost always)	29.5 [7.3]	29.2 [6.3]	0.33 (-1.84 to 2.50)	0.0 (-0.3 to 0.4)
HADS -A ('Anxiety 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 3 months after intervention.	6.2 [2.3]	6.4 [2.2]	-0.17 (-0.90 to 0.56)	-0.1 (-0.4 to 0.2)
HADS -A ('Anxiety 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 1-2 years after intervention.	5.9 [3.8]	6.2 [4.1]	-0.32 (-1.58 to 0.94)	-0.1 (-0.4 to 0.2)
HADS -D ('Depression 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 3 months after intervention.	4.8 [1.2]	4.8 [1.3]	0.03 (-0.37 to 0.43)	0.0 (-0.3 to 0.3)
HADS -D ('Depression 'subscale of the "Hospital Anxiety and Depression Scale"; 7 items on a 4-point Likert scale (0-3), with higher scores being worse condition): 1-2 years after intervention.	4.8 [4.2]	4.9 [4.0]	-0.14 (-1.45 to 1.17)	0.0 (-0.4 to 0.3)
KKG-INT ('Internal control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	26.2 [5.3]	25.1 [4.4]	1.07 (-0.48 to 2.62)	0.2 (-0.1 to 0.5)
KKG-INT ('Internal control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	26.3 [4.3]	25.2 [4.9]	1.10 (-0.38 to 2.58)	0.2 (-0.1 to 0.6)
KKG-EXT ('External control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	21.0 [5.7]	21.2 [5.1]	-0.17 (-1.90 to 1.56)	0.0 (-0.4 to 0.3)
KKG-EXT ('External control 'subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	21.0 [5.5]	20.7 [6.8]	0.26 (-1.73 to 2.25)	0.0 (-0.3 to 0.4)
KKG-FATA ('Fatalistic' subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 3 months after intervention	**16.8 [6.3]**	**19.5 [6.1]**	**-2.72 (-4.71 to -0.73)**	**-0.4 (-0.8 to -0.1)**
KKG-FATA ('Fatalistic' subscale of the "Illness -specific locus of control"; 7 items on a 6-point Likert scale (range1=totally not correct to 6=totally correct): 1-2 years after intervention	18.5 [6.7]	18.4 [6.5]	0.10 (-2.03 to 2.23)	0.0 (-0.3 to 0.3)

Appendix Table 105. Effectiveness of cognitive-behavioral minimal contact program for migraine prevention in adults compared to educational brochure (results from medium risk of bias randomized controlled clinical trial) (continued)

Definition of the Outcome	Mean [Standard Deviation] with Cognitive-behavioral Minimal Contact Program	Mean [Standard Deviation] with Educational Brochure	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Satisfied with treatment (assessed in a telephone interview three months after the intervention. Patients rated the extent of helpfulness of the treatment in reducing medication intake and whether and to what extent they would recommend the treatment to a friend on a range of 1-6 (1=very good to 6=very bad)	**1.7 [0.6]**	**2.8 [1.0]**	**-1.10 (-1.37 to -0.83)**	**-1.3 (-1.7 to -1.0)**
Satisfied that treatment is helpful for reducing medication intake (assessed in a telephone interview three months after the intervention. Patients rated the extent of helpfulness of the treatment in reducing medication intake and whether and to what extent they would recommend the treatment to a friend on a range of 1-6 (1=very good to 6=very bad)	**1.9 [0.6]**	**2.6 [0.8]**	**-0.68 (-0.91 to -0.45)**	**-1.0 (-1.3 to -0.6)**

Bold = significant differences at 95% CI when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D106. Reduction in acute drug overuse with headache school for migraine prevention in adults on acute drug utilization (results from medium risk of bias randomized controlled clinical trial)[212]

Definition of the Outcome	Events/Randomized with Headache School	Events/Randomized with Usual Care	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events per 1000 Treated (95% CI)
Analgesic overuse: at 6 months (number of patients using a given abortive agent or class of abortive agents >3 days/week for >4 weeks)	**0/50**	**18/50**	**0.0 (0.0 to 0.4)**	**-0.36 (-0.49 to -0.23)**	**-3 (-4- to -2)**	**360 (225 to 495)**

Bold = significant differences at 95% CI when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D107. Effectiveness of headache school for migraine prevention in adults (results from medium risk of bias randomized controlled clinical trial)[212]

Definition of the Outcome	Mean [Standard Deviation] with Headache School	Mean [Standard Deviation] with Usual Care	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Mean Migraine Disability Assessment (MIDAS): change relative to baseline	**15.0 [24.0]**	**54.0 [14.0]**	**-39.00 (-46.70 to -31.30)**	**-2.0 (-2.5 to -1.5)**
Mean functionally incapacitating headache days per month	**3.0 [2.6]**	**4.6 [1.7]**	**-1.60 (-2.46 to -0.74)**	**-0.7 (-1.1 to -0.3)**

Bold = significant differences at 95% CI when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D108. Migraine cessation with specialized pharmaceutical care for migraine compared to standard counseling in adults (results from low risk of bias randomized controlled clinical trial)[215]

Definition of the Outcome	Events/Randomized with Active Intervention	Events/Randomized with Control Intervention	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
No headache during the preceding 4 weeks	21/201	16/209	1.4 (0.7to 2.5)	0.03 (-0.03 to 0.08)

CI = confidence interval

Appendix Table D109. Effectiveness of specialized pharmaceutical care for migraine compared to standard counseling for migraine prevention in adults (results from low risk of bias randomized controlled clinical trial)[215]

Definition of the Outcome	Mean [Standard Deviation] with Active Intervention	Mean [Standard Deviation] with Control Intervention	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Days/month with headache	6.1 [6.7]	6.4 [6.9]	-0.30 (-1.61 to 1.01)	0.0 (-0.2 to 0.1)
Headache attacks/month	4.6 [6.1]	5.1 [7.3]	-0.43 (-1.74 to 0.88)	-0.1 (-0.3 to 0.1)
Intensity of pain: Untreated (on an analog scale of 1 (no headache) to 10 (extremely intense headache)	6.8 [3.4]	7.3 [2.9]	-0.46 (-1.07 to 0.15)	-0.1 (-0.3 to 0.0)
Intensity of pain: Treated (on an analog scale of 1 (no headache) to 10 (extremely intense headache)	3.3 [2.7]	3.5 [2.8]	-0.19 (-0.73 to 0.35)	-0.1 (-0.3 to 0.1)
Self-efficacy (Definitions of Schwarzer et al. Higher the score better the self-efficacy)	83.8 [7.5]	84.5 [8.2]	-0.78 (-2.30 to 0.74)	-0.1 (-0.3 to 0.1)
Quality of life: physical health (SF-36)	43.0 [10.3]	44.4 [9.1]	-1.37 (-3.25 to 0.51)	-0.1 (-0.3 to 0.1)
Quality of life: mental health (SF-36)	49.4 [9.1]	49.5 [10.4]	-0.09 (-1.98 to 1.80)	0.0 (-0.2 to 0.2)

Appendix Table D110. Effectiveness of intensive pharmaceutical care campaign for migraine prevention in adults (results from low risk of bias randomized controlled clinical trial)[214]

Definition of the Outcome	Mean [Standard Deviation] with Intensive Pharmaceutical Care Campaign	Mean [Standard Deviation] with Usual Pharmacy Service	Reported Results
3 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	2.5 [Not reported]	2.5 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(2.45, 2.61), control=(2.29, 2.64)
3 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	7.1 [Not reported]	7.1 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(6.66,7.51), control=(6.49,7.65)
6 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	1.3 [Not reported]	1.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(1.21, 1.39), control=(1.19, 1.46)
6 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	5.3 [Not reported]	5.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(5.04, 5.61), control=(4.75, 5.89)
9 months: Incident users (No prescription 9 months before index date): Patients' triptan consumption (doses per month)	0.8 [Not reported]	0.8 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(0.73, 0.97), control=(0.78, 0.90)
9 months: Prevalent users (One or more prescriptions 9 months before index date): Patients' triptan consumption (doses per month)	4.2 [Not reported]	4.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(3.89, 4.51), control=(3.87, 4.72)
9 months: Prevalent users (One or more prescriptions 9 months before index date): <6 doses per month: Patients' triptan consumption (doses per month)	3.0 [Not reported]	3.0 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(2.78, 3.17), control=(2.71, 3.20)
9 months: Prevalent users (One or more prescriptions 9 months before index date): ≥6 and <15 doses per month: Patients' triptan consumption (doses per month)	9.9 [Not reported]	9.3 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(9.3, 10.5), control=(10.4, 11.2)
9 months: Prevalent users (One or more prescriptions 9 months before index date): ≥15 doses per month: Patients' triptan consumption (doses per month)	25.4 [Not reported]	26.0 [Not reported]	Geometric mean. Sample size for incident users: intervention=269 and control=348; 95% CI for intervention=(20.9, 31.0), control=(22.4, 30.1)

Appendix Table D111. Funding, ethical approval, and disclosure of conflict of interest in placebo controlled randomized controlled clinical trials of drugs for migraine prevention that included adverse effects

Drugs	Funded by Grant	Funded by Industry	Funding not Reported	Clear Reporting of Consent	COI not Disclosed	No COI	Disclosed COI	Total
Topiramate	0	6	5	9	6	0	5	11
Divalproex	0	2	0	2	0	0	2	2
Valproate	0	0	1	1	1	0	0	1
Propranolol	0	0	4	3	4	0	0	4
Timolol	0	0	1	1	1	0	0	1
Lamotrigine	0	0	1	1	1	0	0	1
Carbamazepine	0	1	0	0	1	0	0	1
Gabapentin	0	0	2	1	2	0	0	2
Acetazolamide	1	0	0	1	1	0	0	1
Amitriptyline	0	3	0	3	3	0	0	3
Nadolol	0	0	1	1	1	0	0	1
Metoprolol	0	0	3	3	3	0	0	3
Atenolol	0	0	2	0	2	0	0	2
Alprenolol	0	1	0	0	1	0	0	1
Pindolol	0	0	1	0	1	0	0	1
Captopril	0	0	1	0	1	0	0	1
Lisinopril	0	1	0	1	0	0	1	1
Telmisartan	0	1	0	1	0	0	1	1
Candesartan	0	1	0	1	0	0	1	1
Nimodipine	0	1	3	2	4	0	0	4
Verapamil	0	1	0	1	1	0	0	1
Nicardipine	0	1	0	1	1	0	0	1
Nifedipine	0	1	1	2	2	0	0	2
Clonidine	0	3	3	5	6	0	0	6
Dihydroergocryptine	0	0	1	0	1	0	0	1
Dihydroergotamine	0	1	2	3	2	1	0	3
Lisuride	0	0	1	0	1	0	0	1
Methysergide	0	0	1	0	1	0	0	1
Tizanidine	0	1	0	1	1	0	0	1
Montelukast	0	1	0	1	0	0	1	1
Femoxetine	2	0	1	2	3	0	0	3
Fluoxetine	0	2	2	4	4	0	0	4
Indomethacin	0	1	0	0	1	0	0	1
Induprofen	0	0	1	1	1	0	0	1
Ketoprofen	0	1	0	0	1	0	0	1
Naproxen sodium	1	0	1	1	2	0	0	2
Oxcarbazepine	0	1	0	1	0	0	1	1
Tolfenamic Acid	0	1	0	0	1	0	0	1
Tonabersat	0	1	0	1	1	0	0	1
Mg	0	0	2	2	2	0	0	2
Total*	4	34	45	59	70	1	12	83

*-Total includes flunarizine trials

Appendix Table D112. Patient characteristics in placebo controlled randomized controlled clinical trials of adverse effects with drugs for migraine prevention in adults

Drug	# RCTs	Mean Age in Years	# RCTs	% Women	# RCTs	% with Aura	# RCTs	Migraine Frequency/Month	Total RCTs
Topiramate	10	40.7	10	71.6	5	19.8	10	7.01	11
Divalproex	2	43.1	2	78.3	2	4	2	1.5	2
Valproate	1	34	1	79.3	1	86.3	1	4	1
Propranolol	3	37.6	4	82.4	4	22.4	2	3.5	4
Timolol	1	43	1	72	1	4.7	1	5.7	1
Lamotrigine	1	37.2	1	81.8	1	0	1	4.02	1
Gabapentin	2	41.3	2	85.9	1	43.7	2	4.95	2
Acetazolamide	1	39.2	1	75.5	1	9.4	1	5	1
Amitriptyline	2	37.5	3	80	1	0	1	5	3
Nadolol	1	36.3	1	81.3	1	15.6	0		1
Metoprolol	3	38.1	3	83.1	2	0	3	5.59	3
Atenolol	2	41.5	2	74.9	2	0	1	2	2
Alprenolol	1	41.3	1	81.8	1	18.2	1	3	1
Pindolol	1	35.8	1	85.7	1	50	1	2	1
Captopril	1	49	1	58	2	0	2	4.6	1
Lisinopril	1	41	1	81	0		1	2.3	1
Telmisartan	1	39.8	1	84.5	0		1	6.2	1
Candesartan	1	42	1	79	1	0	1	2.97	1
Nimodipine	4	33.5	4	76	4	25	1	4	4
Verapamil	1	33	1	86	0		1	5.3	1
Nicardipine	0		1	73	1	0	1	4.26	1
Nifedipine	1	29.8	1	79	1	0	1	10	2
Clonidine	4	40.1	5	80.8	1	0	1	6	6
Dihydroergotamine	3	38.5	3	72.9	3	21.0	2	4.4	3
Lisuride	0		0		0		1	3.5	1
Methysergide	1	42	1	80	0		1	3	1
Montelukast	1	40	1	88	0		1	5.1	1
Femoxetine	2	40	2	85.8	0		0		3
Fluoxetine	4	38.1	4	77.4	2	22.6	1	7	4
Indomethacin	1	40	1	76	0		0		1
Induprofen	1	35.8	1	60	1	40.3	1	4.8	1
Ketoprofen	1	36	1	88	1	0	1	2.8	1
Magnesium	2	42.4	2	89.5	1	0	2	5	2
Naproxen sodium	2	39.2	2	85	1	0	0		2
Oxcarbazepine	1	40.5	1	84.7	0		1	6	1
Tizanidine	1	40.3	1	79	0		0		1
Tolfenamic Acid	1	35	1	87	1	0	0		1
Tonabersat	1	36	1	92.3	0		0		1

RCTs = number of randomized controlled clinical trials that reported baseline variables

Appendix Table D113. Followup characteristics in placebo controlled randomized controlled clinical trials of adverse effects with drugs for migraine prevention in adults

Drug	Mean Length of followup in Weeks	# RCTs	Mean % Lost to followup	# RCTs
Topiramate	17.9	10	8.4	4
Divalproex	12	2	1.8	2
Valproate	16	1	0	1
Propranolol	12	3	17.3	4
Timolol	16	1	Not reported	Not reported
Lamotrigine	12	1	0	1
Carbamazepine	12	1	6.3	1
Gabapentin	12	2	3.1	2
Acetazolamide	12	1	0	1
Amitriptyline	17	3	28.5	3
Nadolol	12	1	Not reported	Not reported
Metoprolol	13.3	3	Not reported	Not reported
Atenolol	27	2	Not reported	Not reported
Alprenolol	13	1	Not reported	Not reported
Pindolol	11	1	Not reported	Not reported
Captopril	68	1	Not reported	Not reported
Lisinopril	7.5	1	22	1
Telmisartan	12	1	17	1
Candesartan	32	1	5	1
Nimodipine	13	4	8.6	3
Verapamil	20	1	20	1
Nicardipine	16	1	14	1
Nifedipine	16	2	32	2
Clonidine	26	6	29.3	5
Dihydroergocryptine	16	1	Not reported	Not reported
Dihydroergotamine	14.7	3	5.7	3
Lisuride	12	1	0	1
Methysergide	24	1	32.4	1
Montelukast	20	1	2.2	1
Femoxetine	14.7	3	24.5	3
Fluoxetine	15	4	22.2	4
Indomethacin	4	1	Not reported	Not reported
Induprofen	12	1	Not reported	Not reported
Ketoprofen	12	1	Not reported	Not reported
Magnesium	14	2	13.5	2
Naproxen sodium	19	2	15	1
Oxcarbazepine	15	1	3.5	1
Tizanidine	12	1	Not reported	Not reported
Tolfenamic Acid	22	1	Not reported	Not reported
Tonabersat	13	1	5.1	1
Total	17.35	81		

RCTs = number of randomized controlled clinical trials that reported baseline variables

Appendix Table D114. Risk of bias in placebo controlled randomized controlled clinical trials of adverse effects with drugs for migraine prevention

Drugs	High	Low	Medium	Total	% Low
Topiramate	0	6	5	11	54.5
Divalproex	0	1	1	2	50
Valproate	0	0	1	1	0
Propranolol	0	1	3	4	25
Timolol	0	0	1	1	0
Lamotrigine	0	1	0	1	100
Carbamazepine	0	0	1	1	0
Acetazolamide	0	1	0	1	100
Amitriptyline	0	0	3	3	0
Nadolol	0	1	0	1	100
Metoprolol	0	0	3	3	0
Atenolol	0	0	2	2	0
Alprenolol	0	0	1	1	0
Pindolol	0	0	1	1	0
Captopril	0	1	0	1	100
Lisinopril	0	1	0	1	100
Telmisartan	1	0	0	1	0
Candesartan	0	1	0	1	100
Nimodipine	0	1	3	4	25
Verapamil	0	0	1	1	0
Nicardipine	0	0	1	1	0
Nifedipine	1	0	1	2	0
Clonidine	1	1	4	6	16.67
Dihydroergocryptine	0	0	1	1	0
Dihydroergotamine	0	1	2	3	33.33
Lisuride	0	0	1	1	0
Methysergide	0	0	1	1	0
Tizanidine	0	0	1	1	0
Montelukast	0	1	0	1	100
Femoxetine	0	0	3	3	0
Fluoxetine	1	0	3	4	0
Gabapentin	0	0	2	2	0
Indomethacin	0	0	1	1	0
Induprofen	0	0	1	1	0
Ketoprofen	0	0	1	1	0
Naproxen sodium	2	0	0	2	0
Magnesium	0	2	0	2	100
Oxcarbazepine	0	1	0	1	100
Tolfenamic Acid	0	0	1	1	0
Tonabersat	0	1	0	1	100
TOTAL*(includes flunarizine trials)	7	22	54	83	26.51

Appendix Table D115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Botulinum toxin type A 25 U	Guyron, 2004[217] Non-RCT: Case reports	Not reported	Not reported	Depression of temple area (Patient reported)	28.3
Botulinum toxin type A 25 U	Guyron, 2004[217] Non-RCT: Case reports	Not reported	Not reported	Deformity (Physician examined)	100.0
Botulinum toxin type A (and Lidocaine 2 mL) 50 U	Omoigui, 2005[218] Non-RCT: Case reports	Not reported	Not reported	Ptosis	100.0
Zonisamide Initiated with 25 mg/day and titrated up to 100 mg/day	Villani, 2011[219] Non-RCT: Uncontrolled prospective observational study	24	Migraine (International Headache Society)	Difficulty concentrating (transient)	5.9
Zonisamide Initiated with 25 mg/day and titrated up to 100 mg/day	Villani, 2011[219] Non-RCT: Uncontrolled prospective observational study	24	Migraine (International Headache Society)	Mood disorders (transient)	5.9
Zonisamide Initiated with 100 mg/day and titrated up to 300 mg/day	Ashkenazi, 2006[220] Non-RCT: Retrospective uncontrolled study (chart review)	Unclear	Episodic migraine or Transformed migraine according to the Silberstein-Lipton criteria	All	42.4
Zonisamide Initiated with 100 mg/day and titrated up to 300 mg/day	Ashkenazi, 2006[220] Non-RCT: Retrospective uncontrolled study (chart review)	Unclear	Episodic migraine or Transformed migraine according to the Silberstein-Lipton criteria	Fatigue	12.1
Lamotrigine 500 mg/die for I wk and 1000 mg/die for 24 wks	Pizza, 2011[221] Non-RCT: Uncontrolled study	25	Not reported	Somnolence, lack of concentration and a modest gastralgia	53.8
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	All	47.8
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Drowsiness	22.4
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Dizziness	5.9
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Slowness	11.9

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Constipation	5.9
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Ataxia	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Swollen face/body	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Weight gain	3.0
Gabapentin 900-1800 mg	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Mean: 28.8 (range: 12-48)	Migraine (International Headache Society - 2 criteria)	Discontinuation due to adverse effects	22.4
Divalproex Mean: 974 mg /day	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Nausea	42.0
Divalproex Mean: 974 mg /day	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Infection	39.0
Divalproex Mean: 974 mg /day	Vukovic, 2009[222] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Alopecia	31.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Tremor	28.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Asthenia	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Dyspepsia	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Somnolence	25.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Pharyngitis	23.0

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Flu-like syndrome	21.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Pain	19.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Weight gain	19.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Abdominal pain	18.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Back pain	17.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Dizziness	17.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Diarrhea	16.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Rhinitis	15.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Nervousness	11.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Vomiting	11.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Insomnia	10.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Myalgia	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Sinusitis	9.0

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Depression	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Neck pain	9.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Bronchitis	8.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Increased appetite	8.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Accidental injury	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Allergic reaction	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Chest pain	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Increased cough	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Constipation	7.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Arthralgia	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Rash	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Ecchymosis	6.0
Divalproex Mean: 974 mg /day	Silberstein, 1999[223] Non-RCT: Prospective uncontrolled open-label	Up to 144 (3y)	Migraine (International Headache Society)	Flatulence	6.0

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Valproic acid 300 to 1200 mg per day	Kinze, 2001[224] Non-RCT: Prospective open-label	24	Migraine (International Headache Society)	Discontinuation due to hair loss	1.9
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Sleepiness	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Nausea	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Blurry vision	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Sluggish	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Libido	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Upset stomach	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Confusion	6.3
Valproic acid Adjusted to maintain blood levels between 50	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	All adverse effects	50.0

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
and 100 µg/mL (mean 61 µg/m)					
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Nausea	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to GI Upset	12.5
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Confusion	6.3
Valproic acid Adjusted to maintain blood levels between 50 and 100 µg/mL (mean 61 µg/m)	Vijayan, 1995[225] Non-RCT: Prospective cohort	Variable (Up to 52)	Chronic daily headache	Discontinuation due to Sleepiness	6.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Discontinuation due to adverse effects	12.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	3.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	50.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	5.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other	5.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	2.8
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	77.8
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	13.9
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other adverse effects	8.3

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Abnormal liver function test	3.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Weight gain	33.3
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Tremor	10.0
Sodium valproate 600 to 1000 mg daily	Ghose, 1999[226] Non-RCT: Prospective, open-label	240 (5y)	Migraine with or without aura	Other adverse effects	6.7
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Drowsiness, tiredness, weakness	13.7 vs. 20.5
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Dryness of mouth, sore tongue, bad taste	0.0 vs. 13.7
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Giddiness, ataxia	19.6 vs. 0.0
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Faintness, dizziness	5.9 vs. 6.8
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Nausea	11.8 vs. 6.8
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Increased appetite	2.0 vs. 0.0
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Epigastric discomfort	2.0 vs. 1.4
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Cramps, limb pains	3.9 vs. 1.4

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Irritability, agitation	3.9 vs. 2.7
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Insomnia, nightmare	2.0 vs. 1.4
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Bruising, prominent veins	0.0 vs. 1.4
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Skin itching, rash	3.9 vs. 0.0
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Blurred vision	3.9 vs. 0.0
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Lack of concentration	3.9 vs. 0.0
Carbamazepine 200 mg three times daily vs. Clonidine 75 µg three times daily	Anthony, 1972[227] Non-RCT: Controlled trial	Variable (up to 72 for Clonidine and to 16 for Carbamazepine)	Migraine (Friedman's Criteria, 1962)	Swelling of throat	2.0 vs. 0.0
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to adverse effects	4.7
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to incident asthma (not previously experienced)	0.1
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to hypotension with or without bradicarida	2.5

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to Excessive weight gain	0.8
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to Congestive heart failure	0.2
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to Insomnia	0.7
Propranolol 40 mg four times a day (three times a day below age 10)	Rosen, 1983[228] Non-RCT: Prospective cohort	48	Not reported	Discontinuation due to Severe psychological depression	0.3
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Bradicarida	4.4
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Insomnia	1.5
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Depression	1.5
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Precardialgia	1.5 vs. 2.8
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Dizziness	2.9 vs. 0.0
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Paresthesia	0.0 vs. 8.3

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Gastralgia	0.0 vs. 5.6
Propranolol 40mg vs. Metoprolol 40mg	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Bradycardia	4.4 vs. 16.7
Propranolol 40mg vs. Metoprolol 40mg	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Hypotension	0.0 vs. 10.0
Propranolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to adverse effects	11.8 vs. 16.7
Propranolol 40mg vs. Metoprolol 40mg	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to adverse effects	11.8 vs. 26.7
Metoprolol 40mg vs. Methysergide 6 to 10 mg/day	Steardo, 1982[229] Non-RCT: Controlled open-label	24	Migraine (ad hoc Committee)	Discontinuation due to adverse effects	26.7 vs. 16.7
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	All adverse effects	45.0
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Discontinuation due to adverse effects	10.0
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Angina pectoris	0.7
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Intermittent claudication	1.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Lower limb pains	2.6

Appendix Table 115. Adverse effects with drugs for migraine prevention in adults, results from nonrandomized studies (continued)

Drugs, Daily Doses	Reference, Design	Total Length of followup, Weeks	Migraine Definition	Definition of the Adverse Effects	Rate ,%
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Upper limb pains	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Swelling of ankles	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): venules over nose and cheeks	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Facial flushing	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Vomiting	2.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Abdominal cramps	0.7
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Rash	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Scalp hair falling out	0.3
Methysergide 6 mg daily	Curran, 1964[230] Non-RCT: Prospective cohort	Variable ("3 or less to 13 or more (month)")	Not reported	Adverse effects (Severe): Vertigo and ataxia	1.0
Ergotamine NR	Kim, 2005[231] Non-RCT: Case report	Not applicable	Not reported	Upper extremity ischemia	100.0

Appendix Table D116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Any adverse effect	6U 12 weeks	Saper, 2007[4] Low	8/45	3/11	0.7 (0.2 to 2.1)	2.35	-0.10 (-0.38 to 0.19)	3.06
Any adverse effect	7.5U 16 weeks	Elkind, 2006[7] Low	52/105	17/36	1.0 (0.7 to 1.6)	6.71	0.02 (-0.17 to 0.21)	4.58
Any adverse effect	9U 12 weeks	Saper, 2007[4] Low	11/49	3/12	0.9 (0.3 to 2.7)	2.48	-0.03 (-0.30 to 0.25)	3.25
Any adverse effect	10U 12 weeks	Saper, 2007[4] Low	9/44	3/11	0.8 (0.2 to 2.3)	2.42	-0.07 (-0.36 to 0.22)	3.02
Any adverse effect	25U 16 weeks	Elkind, 2006[7] Low	47/101	16/34	1.0 (0.7 to 1.5)	6.57	-0.01 (-0.20 to 0.19)	4.49
Any adverse effect	25U 12 weeks	Saper, 2007[4] Low	17/49	3/12	1.4 (0.5 to 4.0)	2.67	0.10 (-0.18 to 0.38)	3.15
Any adverse effect	50U 16 weeks	Elkind, 2006[7] Low	60/106	17/36	1.2 (0.8 to 1.8)	6.82	0.09 (-0.10 to 0.28)	4.59
Any adverse effect	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	97/174	13/59	2.5 (1.5 to 4.2)	5.86	0.34 (0.21 to 0.47)	5.77
Any adverse effect	80U 12 (one time injection) weeks	Petri*, 2009[9] High	4/32	5/32	0.8 (0.2 to 2.7)	2.16	-0.03 (-0.20 to 0.14)	4.94
Any adverse effect	139U 12 (one time injection) weeks	Cady, 2008[13] Low	0/40	0/19	2.6 (1.5 to 4.4)	5.68	0.00 (-0.08 to 0.08)	6.77
Any adverse effect	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	92/168	12/57	2.2 (1.6 to 3.0)	7.48	0.34 (0.21 to 0.47)	5.75
Any adverse effect	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005t[10] Low	88/173	42/182	2.2 (1.5 to 3.1)	7.12	0.28 (0.18 to 0.37)	6.41
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (two injections over the	Aurora, 2010[1] Medium	86/341	39/338	2.4 (1.8 to 3.3)	7.51	0.14 (0.08 to 0.19)	7.06

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	course: week 1, week 12; open label three injections: week 24, 36, 48) weeks							
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	116/347	49/358	1.3 (1.1 to 1.5)	8.56	0.20 (0.14 to 0.26)	7
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: wk 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	203/341	156/338	2.8 (2.1 to 3.8)	7.5	0.13 (0.06 to 0.21)	6.8
Any adverse effect	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	113/187	39/182	1.2 (1.0 to 1.3)	8.67	0.39 (0.30 to 0.48)	6.5
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	226/347	202/358	2.0 (0.9 to 4.7)	3.54	0.09 (0.02 to 0.16)	6.84
Any adverse effect	210U 12 (one time injection) weeks	Petri*, 2009[9] High	12/32	6/32	3.1 (1.9 to 5.1)	5.89	0.19 (-0.03 to 0.40)	4.11
Any adverse effect	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	119/182	13/62	(Excluded) (0.0 to 0.0)		0.44 (0.32 to 0.57)	5.9
Any adverse effect	**All doses**	**Pooled**	**1360/2863**	**637/2168**	**1.6 (1.3 to 2.0)**	**100**	**0.16 (0.09 to 0.22)**	**100**

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Back pain	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	3/174	0/59	2.4 (0.1 to 45.8)	17.6	0.02 (-0.01 to 0.05)	20.51
Back pain	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.3 (0.0 to 8.1)	15.48	-0.05 (-0.17 to 0.08)	1.28
Back pain	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	4/168	0/57	3.1 (0.2 to 56.5)	18.12	0.02 (-0.01 to 0.06)	17.03
Back pain	11 U to 260U per treatment weeks	Aurora, 2007[15] Medium	3/187	1/182	2.9 (0.3 to 27.8)	30.12	0.01 (-0.01 to 0.03)	44.76
Back pain	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	6/182	0/62	4.5 (0.3 to 78.3)	18.68	0.03 (0.00 to 0.07)	16.41
Back pain	All doses	Pooled	16/731	2/381	2.2 (0.6 to 7.7)	100	0.02 (0.00 to 0.03)	100
Discontinuations related to adverse effects	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	12/347	5/358	2.5 (0.9 to 7.0)	58.96	0.02 (0.00 to 0.04)	51.23
Discontinuations related to adverse effects	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	14/341	3/338	4.6 (1.3 to 16.0)	41.04	0.03 (0.01 to 0.06)	48.77
Discontinuations related to adverse effects	**All doses**	**Pooled**	**26/688**	**8/696**	**3.2 (1.4 to 7.1)**	**100**	**0.03 (0.01 to 0.04)**	**100**
Dizziness	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.3 (0.0 to 8.1)	16.12	-0.05 (-0.17 to 0.08)	3.06

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Dizziness	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	2/43	0/21	2.5 (0.1 to 49.9)	17.79	0.05 (-0.05 to 0.14)	5.31
Dizziness	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	1/173	3/182	0.4 (0.0 to 3.3)	31.37	-0.01 (-0.03 to 0.01)	43.71
Dizziness	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	4/187	0/182	8.8 (0.5 to 161.6)	18.76	0.02 (0.00 to 0.05)	41.31
Dizziness	240U 12 (one time injection) weeks	Chankrachang*, *2011[8] Low	1/43	0/21	1.5 (0.1 to 35.3)	15.96	0.02 (-0.06 to 0.11)	6.61
Dizziness	All doses	Pooled	8/466	4/427	1.1 (0.3 to 4.1)	100	0.01 (-0.02 to 0.03)	100
Dysphagia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	3/174	0/59	2.4 (0.1 to 45.8)	23.99	0.02 (-0.01 to 0.05)	25.86
Dysphagia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	5/168	0/57	3.8 (0.2 to 67.2)	25.16	0.03 (-0.01 to 0.07)	19.36
Dysphagia	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	4/173	0/182	9.5 (0.5 to 174.5)	24.56	0.02 (0.00 to 0.05)	40.45
Dysphagia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	11/182	0/62	7.8 (0.5 to 130.3)	26.29	0.06 (0.02 to 0.10)	14.33
Dysphagia	**All doses**	**Pooled**	**23/697**	**1/360**	**5.1 (1.2 to 21.8)**	**100**	**0.03 (0.01 to 0.04)**	**100**

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Eyelid edema	7.5U 16 weeks	Elkind, 2006[7] Low	1/105	0/36	1.0 (0.0 to 25.1)	18.17	0.01 (-0.03 to 0.05)	21.56
Eyelid edema	25U 16 weeks	Elkind, 2006[7] Low	0/101	0/34	5.2 (0.3 to 88.6)	20.8	0.00 (-0.04 to 0.04)	22.27
Eyelid edema	50U 16 weeks	Elkind, 2006[7] Low	7/106	0/36	0.5 (0.0 to 7.8)	21.78	0.07 (0.01 to 0.13)	15.8
Eyelid edema	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	1/43	1/21	24.3 (1.5 to 408.0)	20.96	-0.02 (-0.12 to 0.08)	8.51
Eyelid edema	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	12/187	0/182	0.2 (0.0 to 4.1)	18.3	0.06 (0.03 to 0.10)	24.28
Eyelid edema	240U 12 (one time injection) weeks	Chankrachang*, *2011[8] Low	0/43	1/21	(Excluded) (0.0 to 0.0)		-0.05 (-0.15 to 0.06)	7.59
Eyelid edema	All doses	Pooled	21/585	1/330	1.7 (0.3 to 9.7)	100	0.02 (-0.01 to 0.06)	100
Headache	6U 12 weeks	Saper, 2007[4] Low	2/45	0/11	1.2 (0.1 to 23.2)	1.84	0.04 (-0.10 to 0.18)	1.94
Headache	7.5U 16 weeks	Elkind, 2006[7] Low	1/105	1/36	0.3 (0.0 to 5.3)	2.15	-0.02 (-0.08 to 0.04)	11.71
Headache	9U 12 weeks	Saper, 2007[4] Low	0/49	1/12	0.1 (0.0 to 2.0)	1.64	-0.08 (-0.26 to 0.09)	1.22
Headache	10U 12 weeks	Saper, 2007[4] Low	1/44	0/11	0.8 (0.0 to 18.4)	1.64	0.02 (-0.10 to 0.15)	2.43
Headache	25U 12 weeks	Saper, 2007[4] Low	3/49	1/12	0.7 (0.1 to 6.5)	3.42	-0.02 (-0.19 to 0.15)	1.31
Headache	25U 16 weeks	Elkind, 2006[7] Low	2/101	1/34	0.7 (0.1 to 7.4)	2.88	-0.01 (-0.07 to 0.05)	9.99
Headache	50U 16 weeks	Elkind, 2006[7] Low	8/106	1/36	2.7 (0.4 to 21.0)	3.87	0.05 (-0.03 to 0.12)	6.99
Headache	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	7/174	3/59	0.8 (0.2 to 3.0)	9.29	-0.01 (-0.07 to 0.05)	9.46
Headache	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.1)	1.62	-0.05 (-0.15 to 0.06)	3.39
Headache	150 U 24 (three	Silberstein, 2005[11]	14/168	3/57	1.6 (0.5 to 5.4)	11.04	0.03	7.57

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	injection at day 0, day 90, and day 180) weeks	Low					(-0.04 to 0.10)	
Headache	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	12/173	11/182	1.1 (0.5 to 2.5)	25.84	0.01 (-0.04 to 0.06)	14.36
Headache	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	11/187	9/182	1.2 (0.5 to 2.8)	22.03	0.01 (-0.04 to 0.06)	17.75
Headache	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	15/182	3/62	1.7 (0.5 to 5.7)	11.13	0.03 (-0.03 to 0.10)	8.5
Headache	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	0/43	1/21	0.2 (0.0 to 4.1)	1.62	-0.05 (-0.15 to 0.06)	3.39
Headache	All doses	Pooled	76/1469	33/735	1.1 (0.7 to 1.6)	100	0.01 (-0.02 to 0.02)	100
Hypertonia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	13/174	0/59	9.3 (0.6 to 153.4)	8	0.08 (0.03 to 0.12)	17.89
Hypertonia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	15/168	0/57	10.6 (0.6 to 175.0)	8.04	0.09 (0.04 to 0.14)	15.31
Hypertonia	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	9/173	4/182	2.4 (0.7 to 7.5)	46.94	0.03 (-0.01 to 0.07)	23.81
Hypertonia	110 U to 260 U per treatment	Aurora, 2007[15] Medium	13/187	2/182	6.3 (1.4 to 27.6)	29.01	0.06 (0.02 to 0.10)	23.67

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	weeks							
Hypertonia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Risk of bias Low	13/182	0/62	9.1 (0.6 to 151.6)	8	0.07 (0.03 to 0.12)	19.32
Hypertonia	**All doses**	**Pooled**	**63/884**	**7/542**	**4.4 (2.0 to 9.8)**	**100**	**0.06 (0.04 to 0.08)**	**100**
Neck pain	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	30/174	1/59	10.2 (1.4 to 73.0)	12.65	0.16 (0.09 to 0.22)	12.91
Neck pain	120U 12 (one time injection) weeks	Chankrachang*, 2011[8] Low	2/43	1/21	1.0 (0.1 to 10.7)	10.24	0.00 (-0.11 to 0.11)	9.63
Neck pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	37/168	1/57	12.6 (1.8 to 89.4)	12.7	0.20 (0.13 to 0.27)	12.42
Neck pain	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	23/173	1/182	24.2 (3.3 to 177.2)	12.5	0.13 (0.08 to 0.18)	13.93
Neck pain	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	20/341	0/338	40.6 (2.5 to 669.2)	8.02	0.06 (0.03 to 0.08)	15.51
Neck pain	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	32/187	8/182	3.9 (1.8 to 8.2)	24.5	0.13 (0.07 to 0.19)	13.18
Neck pain	225 U 24 (three injection at day 0,	Silberstein, 2005[11] Low	41/182	1/62	14.0 (2.0 to 99.4)	12.7	0.21 (0.14 to 0.28)	12.66

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	day 90, and day 180) weeks							
Neck pain	240U 12 (one time injection)weeks	Chankrachang*, 2011[8]* Risk of bias Low	0/43	1/21	0.2 (0.0 to 4.1)	6.7	-0.05 (-0.15 to 0.06)	9.76
Neck pain	**All doses**	**Pooled**	**185/1311**	**13/922**	**6.4 (2.5 to 16.4)**	**100**	**0.11 (0.06 to 0.16)**	**100**
Neck rigidity	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	14/174	0/59	9.9 (0.6 to 164.1)	5.8	0.08 (0.03 to 0.13)	18.99
Neck stiffness	100U 16 weeks	Freitag, 2008[5] Low	1/20	1/21	1.1 (0.1 to 15.7)	6.24	0.00 (-0.13 to 0.13)	5.5
Neck rigidity	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	14/168	0/57	10.0 (0.6 to 164.2)	5.8	0.08 (0.04 to 0.13)	18.54
Neck rigidity	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	8/173	2/182	4.2 (0.9 to 19.5)	19.34	0.04 (0.00 to 0.07)	22.59
Neck rigidity	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	19/187	6/182	3.1 (1.3 to 7.5)	56.93	0.07 (0.02 to 0.12)	17.98
Neck rigidity	225 U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	27/182	0/62	18.6 (1.2 to 301.0)	5.89	0.15 (0.09 to 0.21)	16.4
Neck rigidity	**All doses**	**Pooled**	**83/904**	**10/563**	**3.9 (2.0 to 7.7)**	**100**	**0.08 (0.04 to 0.11)**	**100**
Injection site pain	75U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	8/174	3/59	0.9 (0.2 to 3.3)	17.11	-0.01 (-0.07 to 0.06)	3.24
Injection site pain	120U 12 (one time injection)	Chankrachang*, 2011[8]*Low	0/43	1/21	0.3 (0.0 to 8.1)	2.87	-0.05 (-0.17 to 0.08)	1.19

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	weeks							
Injection site pain	150U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	10/168	3/57	0.2 (0.0 to 4.1)	18.19	-0.05 (-0.15 to 0.06)	2.87
Injection site pain	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	4/173	4/182	1.1 (0.3 to 4.0)	15.26	0.01 (-0.06 to 0.08)	13.95
Injection site pain	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	4/187	1/182	1.1 (0.3 to 4.1)	6.02	0.00 (-0.03 to 0.03)	24.43
Injection site pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	17/182	3/62	3.9 (0.4 to 34.5)	20.14	0.02 (-0.01 to 0.04)	2.82
Injection site pain	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	6.8 (0.4 to 131.0)	2.87	0.02 (-0.01 to 0.04)	1.19
Pain	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	3/187	0/182	1.1 (0.2 to 5.1)	3.28	0.00 (-0.03 to 0.03)	30.95
Pain	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	3/173	3/182	1.9 (0.6 to 6.3)	11.38	0.04 (-0.03 to 0.11)	18.49
Pain	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.2 (0.0 to 4.1)	2.9	-0.05 (-0.15 to 0.06)	0.87
Pain	All doses	Pooled	49/1350	20/969	1.2 (0.7 to 2.0)	100	0.01 (0.00 to 0.02)	100
Blepharoptosis	6U 12 weeks	Saper, 2007[4] Low	1/45	0/11	0.8 (0.0 to 18.0)	3.72	0.02 (-0.10 to 0.15)	2.32

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Blepharoptosis	7.5U 16 weeks	Elkind, 2006[7] Low	2/105	0/36	1.7 (0.1 to 35.5)	4.03	0.02 (-0.03 to 0.07)	8.98
Blepharoptosis	9U 12 weeks	Saper, 2007[4] Low	0/49	0/12	2.2 (0.1 to 37.5)	4.5	0.00 (-0.12 to 0.12)	2.59
Blepharoptosis	10U 12 weeks	Saper, 2007[4] Low	0/44	0/11	3.8 (0.2 to 66.5)	4.45	0.00 (-0.12 to 0.12)	2.56
Blepharoptosis	25U 12 weeks	Saper, 2007[4] Low	4/49	0/12	6.7 (0.4 to 112.7)	4.57	0.08 (-0.06 to 0.22)	1.92
Blepharoptosis	25U 16 weeks	Elkind, 2006[7] Low	5/101	0/34	5.9 (0.3 to 99.4)	4.58	0.05 (-0.01 to 0.11)	7.06
Blepharoptosis	25U 12 weeks	Silberstein, 2000[6] Medium	6/42	0/21	7.7 (0.5 to 128.1)	4.62	0.14 (0.02 to 0.27)	2.33
Blepharoptosis	50U 16 weeks	Elkind, 2006[7] Low	8/106	0/36	2.0 (0.3 to 16.6)	8.33	0.08 (0.01 to 0.14)	6.46
Blepharoptosis	75U 12 weeks	Silberstein, 2000[6] Risk of bias Medium	7/40	0/20	4.9 (0.2 to 100.5)	8.52	0.18 (0.04 to 0.31)	2
Blepharoptosis	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	6/174	1/59	2.4 (0.3 to 18.9)	8.89	0.02 (-0.03 to 0.06)	9.83
Blepharoptosis	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	0/21	12.6 (1.7 to 96.1)	26.7	0.00 (-0.07 to 0.07)	5.7
Blepharoptosis	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	7/168	1/57	9.4 (2.9 to 30.3)	8.98	0.03 (-0.02 to 0.08)	9.27
Blepharoptosis	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	12/173	1/182	4.1 (0.5 to 30.8)	4.09	0.02 (-0.02 to 0.07)	10.51
Blepharoptosis	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	29/187	3/182	2.5 (0.1 to 49.9)	4.02	0.06 (0.03 to 0.10)	7.63

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
Blepharoptosis	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	12/182	1/62	(Excluded) (0.0 to 0.0)		0.14 (0.08 to 0.19)	8.85
Blepharoptosis	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	2/43	0/21	(Excluded) (0.0 to 0.0)		0.05 (0.00 to 0.10)	3.77
Blepharoptosis	210U plus 80U 12 (one time injection) weeks	Petri*, 2009[9] High	2/64	0/63	(Excluded) (0.0 to 0.0)		0.05 (-0.05 to 0.14)	8.21
Blepharoptosis	**All doses**	**Pooled**	**103/1615**	**7/839**	**4.7 (2.6 to 8.7)**	**100**	**0.05 (0.03 to 0.07)**	**100**
Muscle weakness	6U 12 weeks	Saper, 2007[4] Low	0/45	0/11	3.4 (0.2 to 56.2)	16.37	0.00 (-0.12 to 0.12)	10.02
Muscle weakness	9U 12 weeks	Saper, 2007[4] Low	0/49	0/12	20.2 (1.3 to 326.0)	16.74	0.00 (-0.11 to 0.11)	10.37
Muscle weakness	10U 12 weeks	Saper, 2007[4] Low	0/44	0/11	30.5 (1.9 to 488.1)	16.84	0.00 (-0.12 to 0.12)	10.01
Muscle weakness	25U 12 weeks	Saper, 2007[4] R Low	6/49	0/12	81.0 (5.0 to 1308.0)	16.71	0.12 (-0.02 to 0.26)	9.1
Muscle weakness	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	29/174	0/59	40.6 (2.5 to 669.2)	16.48	0.17 (0.11 to 0.23)	12.09
Muscle weakness	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	44/168	0/57	38.3 (2.4 to 610.4)	16.87	0.26 (0.19 to 0.33)	11.76
Muscle weakness	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	38/173	0/182	(Excluded) (0.0 to 0.0)		0.22 (0.16 to 0.28)	12.03
Muscle weakness	155U-195U [Follow-the-Pain strategy] 24 (two injections over the	Aurora, 2010[1] Medium	20/341	0/338	(Excluded) (0.0 to 0.0)		0.06 (0.03 to 0.08)	12.87

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Adverse Effect	Dose Weeks of Treatment	Reference Risk of Bias	Events Randomized Onabotulinumtoxin A	Events Randomized Placebo	Relative Risk (95% CI)	Weight (Relative Risk)	Absolute Risk Difference (95% CI)	Weight (Risk Difference)
	course: week 1, week 12; open label three injections: week 24, 36, 48) weeks							
Muscle weakness	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	56/182	0/62	(Excluded) (0.0 to 0.0)		0.31 (0.24 to 0.38)	11.76
Muscle weakness	**All doses**	**Pooled**	**193/1225**	**1/743**	**25.5 (8.2 to 79.5)**	**100**	**0.13 (0.06 to 0.21)**	**100**
Fever	100U 16 weeks	Freitag, 2008[5] Low	0/20	2/21	1.3 (0.4 to 4.3)	5.48	0.02 (-0.09 to 0.13)	9.11
Flu syndrome	25U 16 weeks	Elkind, 2006[7] Low	4/101	3/34	0.4 (0.1 to 1.9)	23.26	-0.05 (-0.15 to 0.05)	18.89
Flu syndrome	50U 16 weeks	Elkind, 2006[7] Low	7/106	3/36	0.8 (0.2 to 2.9)	28.82	-0.02 (-0.12 to 0.09)	19.16
Flu syndrome	7.5U 16 weeks	Elkind, 2006[7] Low	11/105	3/36	0.2 (0.0 to 4.1)	32.7	-0.10 (-0.24 to 0.05)	17.18
Pyrexia	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.1)	4.87	-0.05 (-0.15 to 0.06)	17.83
Pyrexia	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.1)	4.87	-0.05 (-0.15 to 0.06)	17.83
Pyrexia	All doses	Pooled	22/418	12/169	0.6 (0.3 to 1.3)	100	-0.03 (-0.08 to 0.01)	100

Outcomes	P Value for Relative Risk	I Squared for Relative Risk	P Value for Absolute Risk Difference	I Squared for Absolute Risk Difference
Any adverse effect	0	81.20%	0	82.90%
Back pain	0.80	0.00%	0.67	0.00%
Discontinuations related to adverse effects	0.45	0.00%	0.49	0.00%
Dizziness	0.44	0.00%	0.23	28.60%
Dysphagia	0.90	0.00%	0.40	0.00%
Eyelid edema	0.15	41.50%	0.06	52.80%
Headache	0.84	0.00%	0.91	0.00%

Appendix Table 116. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with random effects model, inverse variance weights) (continued)

Outcomes	P Value for Relative Risk	I Squared for Relative Risk	P Value for Absolute Risk Difference	I Squared for Absolute Risk Difference
Hypertonia	0.69	0.00%	0.38	4.70%
Neck pain	0.06	47.70%	0	83.70%
Neck rigidity	0.66	0.00%	0.03	60.80%
Injection site pain	0.67	0.00%	0.80	0.00%
Blepharoptosis	0.96	0.00%	0.06	37.90%
Muscle weakness	0.72	0.00%	0	91.10%
Fever	0.65	0.00%	0.86	0.00%

CI = confidence interval; Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0; * trials of abobotulinumtoxin A

Appendix Table D117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Any adverse effect	6U 12 weeks	Saper, 2007[4] Low	8/45	3/11	0.6 (0.1 to 2.7)	0.027	0.04 (-0.16 to 0.24)	0.03
Any adverse effect	7.5U 16 weeks	Elkind, 2006[7] Low	52/105	17/36	1.1 (0.5 to 2.3)	0.058	0.07 (-0.09 to 0.22)	0.045
Any adverse effect	9U 12 weeks	Saper, 2007[4] Low	11/49	3/12	0.9 (0.2 to 3.8)	0.029	0.07 (-0.13 to 0.26)	0.031
Any adverse effect	10U 12 weeks	Saper, 2007[4] Low	9/44	3/11	6.2 (0.3 to 114.2)	0.009	0.19 (0.05 to 0.33)	0.049
Any adverse effect	25U 16 weeks	Elkind, 2006[7] Low	47/101	16/34	1.0 (0.4 to 2.1)	0.056	0.05 (-0.11 to 0.21)	0.044
Any adverse effect	25U 12 weeks	Saper, 2007[4] Low	17/49	3/12	1.6 (0.4 to 6.7)	0.03	0.13 (-0.07 to 0.32)	0.03
Any adverse effect	50U 16 weeks	Elkind, 2006[7] Low	60/106	17/36	1.5 (0.7 to 3.1)	0.058	0.11 (-0.04 to 0.27)	0.045
Any adverse effect	75 U 24 weeks	Silberstein, 2005[11] Low	97/174	13/59	4.5 (2.2 to 8.8)	0.062	0.30 (0.19 to 0.42)	0.057
Any adverse effect	80U 12 weeks	Petri*, 2009[9] High	4/32	5/32	0.8 (0.2 to 3.2)	0.03	0.02 (-0.12 to 0.17)	0.048
Any adverse effect	139U 12 weeks	Cady, 2008[13] Low	0/40	0/19	0.5 (0.0 to 25.2)	0.005	0.01 (-0.06 to 0.09)	0.067
Any adverse effect	150 U 24 weeks	Silberstein, 2005[11] Low	92/168	12/57	4.5 (2.2 to 9.2)	0.061	0.30 (0.19 to 0.42)	0.056
Any adverse effect	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Risk of bias Low	88/173	42/182	3.5 (2.2 to 5.4)	0.075	0.26 (0.17 to 0.36)	0.063
Any adverse effect	155U-195U [Follow-the-pain strategy] 24 (two injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	86/341	39/338	2.6 (1.7 to 3.9)	0.078	0.14 (0.08 to 0.19)	0.07

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	116/347	49/358	3.2 (2.2 to 4.6)	0.08	0.20 (0.14 to 0.26)	0.069
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (2 injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	203/341	156/338	1.7 (1.3 to 2.3)	0.083	0.14 (0.06 to 0.21)	0.067
Any adverse effect	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	113/187	39/182	5.6 (3.5 to 8.9)	0.075	0.37 (0.28 to 0.45)	0.064
Any adverse effect	155U-195U [Follow-the-Pain strategy] 24 (3 injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	226/347	202/358	1.4 (1.1 to 2.0)	0.083	0.09 (0.02 to 0.16)	0.068
Any adverse effect	210U 12 (one time injection) weeks	Petri*, 2009[9] High	12/32	6/32	2.6 (0.8 to 8.1)	0.039	0.18 (0.01 to 0.35)	0.04
Any adverse effect	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	119/182	13/62	7.1 (3.6 to 14.1)	0.062	0.40 (0.28 to 0.51)	0.058
Any adverse effect	**Pooled**		**1360/2863**	**637/2168**	**2.2 (1.5 to 3.0)**	**1**	**0.16 (0.09 to 0.23)**	**1**
Back pain	75 U 24 (3 injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	3/174	0/59	2.4 (0.1 to 47.7)	0.177	0.02 (-0.01 to 0.04)	0.205

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Back pain	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.148	0.01 (-0.02 to 0.04)	0.013
Back pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	4/168	0/57	3.1 (0.2 to 59.3)	0.182	0.02 (0.00 to 0.04)	0.17
Back pain	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	3/187	1/182	3.0 (0.3 to 28.6)	0.304	0.01 (-0.01 to 0.03)	0.448
Back pain	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	6/182	0/62	4.6 (0.3 to 82.9)	0.188	0.02 (0.00 to 0.05)	0.164
Back pain	**All doses**	**Pooled**	**16/731**	**2/381**	**4.9 (1.2 to 35.7)**	**1**	**0.02 (0.00 to 0.04)**	**1**
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (three injections over the course: week 1, week 12, week 24) weeks	Diener, 2010[2] Low	12/347	5/358	2.5 (0.9 to 7.3)	0.587	0.03 (0.01 to 0.04)	0.512
Discontinuations related to AE	155U-195U [Follow-the-Pain strategy] 24 (2 injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	14/341	3/338	4.8 (1.4 to 16.8)	0.413	0.03 (0.02 to 0.04)	0.488
Discontinuations related to adverse effects	**All doses**	**Pooled**	**26/688**	**8/696**	**3.5 (1.2 to 10.9)**	**1**	**0.03 (0.01 to 0.05)**	**1**
Dizziness	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.156	0.00 (-0.05 to 0.05)	0.031
Dizziness	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	2/43	0/21	2.6 (0.1 to 56.4)	0.174	0.02 (-0.03 to 0.06)	0.053

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Dizziness	105U-260U ("Follow-the-pain" approach) 24 weeks	Mathew, 2005[10] Low	1/173	3/182	0.3 (0.0 to 3.4)	0.32	-0.01 (-0.03 to 0.01)	0.437
Dizziness	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	4/187	0/182	9.0 (0.5 to 167.5)	0.193	0.02 (0.00 to 0.04)	0.413
Dizziness	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	1/43	0/21	1.5 (0.1 to 38.8)	0.157	0.01 (-0.03 to 0.06)	0.066
Dizziness	All doses	Pooled	8/466	4/427	1.8 (0.5 to 8.0)	1	0.01 (-0.02 to 0.04)	1
Dysphagia	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	3/174	0/59	2.4 (0.1 to 47.7)	0.24	0.03 (0.00 to 0.05)	0.258
Dysphagia	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	5/168	0/57	3.9 (0.2 to 71.1)	0.251	0.03 (0.01 to 0.05)	0.193
Dysphagia	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 205[10] Low	4/173	0/182	9.7 (0.5 to 181.3)	0.248	0.03 (0.01 to 0.05)	0.404
Dysphagia	225 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	11/182	0/62	8.4 (0.5 to 144.4)	0.262	0.04 (0.02 to 0.07)	0.144
Dysphagia	**All doses**	**Pooled**	**23/697**	**1/360**			**0.03 (0.01 to 0.05)**	**1**
Eyelid edema	7.5U 16 weeks	Elkind, 2006[7] Low	1/105	0/36	1.0 (0.0 to 26.3)	0.16	0.01 (-0.03 to 0.05)	0.217
Eyelid edema	25U 16 weeks	Elkind, 2006[7] Low	0/101	0/34	0.3 (0.0 to 17.5)	0.121	0.00 (-0.03 to 0.04)	0.225
Eyelid edema	50U 16 weeks	Elkind, 2006[7] Low	7/106	0/36	5.5 (0.3 to 98.8)	0.184	0.05 (0.00 to 0.09)	0.16
Eyelid edema	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	1/43	1/21	0.5 (0.0 to 8.0)	0.189	0.00 (-0.06 to 0.06)	0.081

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Eyelid edema	110 U to 260 U per treatment weeks	Aurora, 2007[15] Medium	12/187	0/182	26.0 (1.5 to 442.4)	0.188	0.06 (0.02 to 0.09)	0.245
Eyelid edema	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	0/43	1/21	0.2 (0.0 to 4.0)	0.159	0.00 (-0.06 to 0.06)	0.072
Eyelid edema	All doses	Pooled	21/585	1/330	5.5 (0.8 to 62.0)	1	0.02 (-0.02 to 0.06)	1
Headache	6U 12 weeks	Saper, 2007[4] Low	2/45	0/11	1.3 (0.1 to 29.5)	0.019	0.01 (-0.05 to 0.06)	0.022
Headache	7.5U 16 weeks	Elkind, 2006[7] Low	1/105	1/36	0.3 (0.0 to 5.5)	0.023	-0.01 (-0.05 to 0.03)	0.118
Headache	9U 12 weeks	Saper, 2007[4] Low	0/49	1/12	0.1 (0.0 to 2.0)	0.017	-0.01 (-0.07 to 0.05)	0.012
Headache	10U 12 weeks	Saper, 2007[4] Low	1/44	0/11	0.8 (0.0 to 20.8)	0.017	0.00 (-0.05 to 0.06)	0.025
Headache	25U 12 weeks	Saper, 2007[4] Low	3/49	1/12	0.7 (0.1 to 7.6)	0.032	0.00 (-0.06 to 0.06)	0.013
Headache	25U 16 weeks	Elkind, 2006[7] Low	2/101	1/34	0.7 (0.1 to 7.6)	0.031	-0.01 (-0.05 to 0.04)	0.096
Headache	50U 16 weeks	Elkind, 2006[7] Low	8/106	1/36	2.9 (0.3 to 23.7)	0.04	0.02 (-0.03 to 0.07)	0.07
Headache	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	7/174	3/59	0.8 (0.2 to 3.1)	0.094	-0.01 (-0.05 to 0.04)	0.095
Headache	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	0/43	1/21	0.2 (0.0 to 4.0)	0.017	-0.01 (-0.07 to 0.04)	0.032
Headache	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	14/168	3/57	1.6 (0.5 to 5.9)	0.109	0.01 (-0.03 to 0.06)	0.075
Headache	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	12/173	11/182	1.2 (0.5 to 2.7)	0.252	0.01 (-0.03 to 0.05)	0.145

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Headache	110U to 260 U per treatment weeks	Aurora, 2007[15] Medium	11/187	9/182	1.2 (0.5 to 3.0)	0.22	0.01 (-0.03 to 0.04)	0.179
Headache	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	15/182	3/62	1.8 (0.5 to 6.3)	0.111	0.02 (-0.03 to 0.06)	0.086
Headache	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.0)	0.017	-0.01 (-0.07 to 0.04)	0.032
Headache	All doses	Pooled	76/1469	33/735	1.0 (0.5 to 1.6)	1	0.00 (-0.02 to 0.03)	1
Hypertonia	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	13/174	0/59	9.9 (0.6 to 170.0)	0.082	0.07 (0.04 to 0.10)	0.179
Hypertonia	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	15/168	0/57	11.6 (0.7 to 197.3)	0.082	0.07 (0.04 to 0.10)	0.153
Hypertonia	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	9/173	4/182	2.4 (0.7 to 8.1)	0.461	0.05 (0.02 to 0.08)	0.238
Hypertonia	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	13/187	2/182	6.7 (1.5 to 30.2)	0.292	0.06 (0.04 to 0.09)	0.236
Hypertonia	22U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	13/182	0/62	10.0 (0.6 to 170.0)	0.082	0.07 (0.04 to 0.10)	0.194
Hypertonia	**All doses**	**Pooled**	**63/884**	**7/542**	**7.3 (3.1 to 20.9)**	**1**	**0.06 (0.04 to 0.09)**	**1**
Neck pain	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	30/174	1/59	12.1 (1.6 to 90.7)	0.128	0.15 (0.09 to 0.21)	0.13
Neck pain	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	2/43	1/21	1.0 (0.1 to 11.4)	0.101	0.04 (-0.05 to 0.13)	0.094

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Neck pain	150 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	37/168	1/57	15.8 (2.1 to 118.1)	0.128	0.19 (0.12 to 0.25)	0.125
Neck pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	23/173	1/182	27.8 (3.7 to 207.9)	0.128	0.13 (0.08 to 0.17)	0.14
Neck pain	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label 3 injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	20/341	0/338	43.2 (2.6 to 716.7)	0.085	0.06 (0.04 to 0.09)	0.156
Neck pain	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	32/187	8/182	4.5 (2.0 to 10.0)	0.233	0.13 (0.07 to 0.18)	0.133
Neck pain	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	41/182	1/62	17.7 (2.4 to 131.9)	0.128	0.19 (0.13 to 0.26)	0.127
Neck pain	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.0)	0.069	0.01 (-0.08 to 0.10)	0.095
Neck pain	**All doses**	**Pooled**	**185/1311**	**13/922**	**9.5 (4.7 to 19.2)**	**1**	**0.11 (0.05 to 0.17)**	**1**
Neck rigidity	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	14/174	0/59	10.8 (0.6 to 183.1)	0.061	0.08 (0.04 to 0.12)	0.19
Neck stiffness	100U 16 weeks	Freitag, 2008[5] Low	1/20	1/21	1.1 (0.1 to 18.1)	0.061	0.06 (-0.01 to 0.12)	0.055
Neck rigidity	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	14/168	0/57	10.8 (0.6 to 183.9)	0.061	0.08 (0.04 to 0.12)	0.185

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Neck rigidity	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	8/173	2/182	4.4 (0.9 to 20.8)	0.201	0.04 (0.01 to 0.07)	0.226
Neck rigidity	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	19/187	6/182	3.3 (1.3 to 8.5)	0.554	0.07 (0.03 to 0.11)	0.18
Neck rigidity	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	27/182	0/62	22.1 (1.3 to 368.0)	0.062	0.12 (0.08 to 0.17)	0.164
Neck rigidity	**All doses**	**Pooled**	**83/904**	**10/563**	**6.2 (2.9 to 14.1)**	**1**	**0.08 (0.04 to 0.11)**	**1**
Injection site pain	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	8/174	3/59	0.9 (0.2 to 3.5)	0.167	0.00 (-0.04 to 0.04)	0.032
Injection site pain	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	0/43	1/21	0.2 (0.0 to 4.0)	0.029	-0.01 (-0.05 to 0.04)	0.011
Injection site pain	150U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	10/168	3/57	1.1 (0.3 to 4.3)	0.176	0.00 (-0.04 to 0.04)	0.029
Injection site pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	4/173	4/182	1.1 (0.3 to 4.3)	0.157	0.00 (-0.03 to 0.03)	0.14
Injection site pain	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	4/187	1/182	4.0 (0.4 to 35.7)	0.064	0.01 (-0.01 to 0.03)	0.245
Injection site pain	225U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 205[11] Low	17/182	3/62	2.0 (0.6 to 7.2)	0.194	0.01 (-0.03 to 0.05)	0.029
Injection site pain	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]*Low	0/43	1/21	0.2 (0.0 to 4.0)	0.029	-0.01 (-0.05 to 0.04)	0.011

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Pain	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	3/187	0/182	6.9 (0.4 to 135.0)	0.035	0.01 (-0.01 to 0.03)	0.31
Pain	105U-260U ("Follow-the-pain" approach) 24 (3 injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	3/173	3/182	1.1 (0.2 to 5.3)	0.119	0.00 (-0.02 to 0.02)	0.185
Pain	100U 16 weeks	Freitag, 2008[5] Low	0/20	1/21	0.3 (0.0 to 8.7)	0.029	-0.01 (-0.05 to 0.04)	0.009
Injection site pain	**All doses**	**Pooled**	**49/1350**	**20/969**	**1.4 (0.7 to 2.5)**	**1**	**0.00 (-0.02 to 0.02)**	**1**
Blepharoptosis	6U 12 weeks	Saper, 2007[4] Low	1/45	0/11	0.8 (0.0 to 20.3)	0.034	0.04 (-0.03 to 0.11)	0.023
Blepharoptosis	7.5U 16 weeks	Elkind, 2006[7] Low	2/105	0/36	1.8 (0.1 to 37.6)	0.038	0.03 (-0.01 to 0.07)	0.089
Blepharoptosis	9U 12 weeks	Saper, 2007[4] Low	0/49	0/12	0.3 (0.0 to 13.4)	0.023	0.03 (-0.03 to 0.10)	0.029
Blepharoptosis	10U 12 weeks	Saper, 2007[4] Low	0/44	0/11	0.3 (0.0 to 13.7)	0.023	0.04 (-0.03 to 0.10)	0.026
Blepharoptosis	25U 12 weeks	Saper, 2007[4] Low	4/49	0/12	2.5 (0.1 to 49.1)	0.04	0.06 (-0.01 to 0.13)	0.021
Blepharoptosis	25U 16 weeks	Elkind, 2006[7] Low	5/101	0/34	3.9 (0.2 to 73.0)	0.042	0.05 (0.00 to 0.10)	0.07
Blepharoptosis	25U 12 weeks	Silberstein, 2000[6] Medium	6/42	0/21	7.7 (0.4 to 142.8)	0.042	0.08 (0.01 to 0.15)	0.023
Blepharoptosis	50U 16 weeks	Elkind, 2006[7] Low	8/106	0/36	6.3 (0.4 to 111.9)	0.043	0.07 (0.02 to 0.12)	0.064
Blepharoptosis	75U 12 weeks	Silberstein, 2000[6] Medium	7/40	0/20	9.2 (0.5 to 169.4)	0.042	0.09 (0.02 to 0.16)	0.02
Blepharoptosis	75U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	6/174	1/59	2.1 (0.2 to 17.6)	0.078	0.03 (-0.01 to 0.06)	0.098
Blepharoptosis	120U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	0/21	0.5 (0.0 to 25.8)	0.023	0.02 (-0.03 to 0.08)	0.057
Blepharoptosis	150U 24 (three injection at day 0,	Silberstein, 2005[11]	7/168	1/57	2.4 (0.3 to 20.2)	0.08	0.03 (-0.01 to 0.07)	0.092

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
	day 90, and day 180) weeks	Low						
Blepharoptosis	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	12/173	1/182	13.5 (1.7 to 104.9)	0.085	0.06 (0.03 to 0.10)	0.104
Blepharoptosis	110U to 260U per treatment weeks	Aurora, 2007[15] Medium	29/187	3/182	11.0 (3.3 to 36.6)	0.246	0.11 (0.07 to 0.16)	0.076
Blepharoptosis	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	12/182	1/62	4.3 (0.5 to 33.8)	0.084	0.05 (0.01 to 0.09)	0.088
Blepharoptosis	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	2/43	0/21	2.6 (0.1 to 56.4)	0.038	0.05 (-0.01 to 0.11)	0.038
Blepharoptosis	210U plus 80U 12 (one time injection) weeks	Petri*, 2009[9] High	2/64	0/63	5.1 (0.2 to 108.0)	0.038	0.04 (-0.01 to 0.08)	0.082
Blepharoptosis	**All doses**	**Pooled**	**103/1615**	**7/839**	**8.0 (3.5 to 21.6)**	**1**	**0.05 (0.03 to 0.08)**	**1**
Muscle weakness	6U 12 weeks	Saper, 2007[4] Low	0/45	0/11	0.3 (0.0 to 13.4)	0.087	0.03 (-0.07 to 0.13)	0.1
Muscle weakness	9U 12 weeks	Saper, 2007[4] Low	0/49	0/12	0.3 (0.0 to 13.4)	0.087	0.03 (-0.07 to 0.12)	0.104
Muscle weakness	10U 12 weeks	Saper, 2007[4] Low	0/44	0/11	0.3 (0.0 to 13.7)	0.087	0.03 (-0.07 to 0.13)	0.1
Muscle weakness	25U 12 weeks	Saper, 2007[4] Low	6/49	0/12	3.7 (0.2 to 71.0)	0.119	0.13 (0.01 to 0.24)	0.091
Muscle weakness	75 U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	29/174	0/59	24.1 (1.5 to 401.3)	0.124	0.16 (0.11 to 0.22)	0.121
Muscle weakness	150 U 24 (three injections at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	44/168	0/57	41.1 (2.5 to 679.2)	0.124	0.25 (0.18 to 0.32)	0.118

Appendix Table 117. Adverse effects with onabotulinumtoxin A vs. placebo for migraine prevention in adults (results from randomized controlled clinical trials were pooled with Bayesian odds ratios and maximum likelihood absolute risk difference) (continued)

Adverse Effect	Dose and Weeks of Treatment	Reference Risk of Bias	Events/ Randomized with Drug	Events/ Randomized with Placebo	Bayesian Odds Ratio (Median, 2.5 and 97.5% CrI)	Weight	Absolute Risk Difference, Maximum Likelihood Method (95% CI)	Weight
Muscle weakness	105U-260U ("Follow-the-pain" approach) 24 (three injections at day 0, day 90, and day 180) weeks	Mathew, 2005[10] Low	38/173	0/182	103.7 (6.3 to 1703.1)	0.124	0.21 (0.15 to 0.27)	0.12
Muscle weakness	155U-195U [Follow-the-Pain strategy] 24 (two injections over the course: week 1, week 12; open label three injections: week 24, 36, 48) weeks	Aurora, 2010[1] Medium	20/341	0/338	43.2 (2.6 to 716.7)	0.124	0.06 (0.03 to 0.09)	0.129
Muscle weakness	225U 24 (three injection at day 0, day 90, and day 180) weeks	Silberstein, 2005[11] Low	56/182	0/62	55.8 (3.4 to 918.6)	0.124	0.29 (0.22 to 0.36)	0.118
Muscle weakness	**All doses**	**Pooled**	**193/1225**	**1/743**			**0.13 (0.06 to 0.21)**	**1**
Fever	100U 16 weeks	Freitag, 2008[5] Low	0/20	2/21	0.2 (0.0 to 4.2)	0.059	-0.05 (-0.11 to 0.01)	0.094
Flu syndrome	25U 16 weeks	Elkind, 2006[7] Low	4/101	3/34	0.4 (0.1 to 2.0)	0.234	-0.04 (-0.10 to 0.01)	0.194
Flu syndrome	50U 16 weeks	Elkind, 2006[7] Low	7/106	3/36	0.8 (0.2 to 3.2)	0.284	-0.03 (-0.09 to 0.02)	0.197
Flu syndrome	7.5U 16 weeks	Elkind, 2006[7] Low	11/105	3/36	1.3 (0.3 to 4.9)	0.316	-0.02 (-0.08 to 0.04)	0.177
Pyrexia	240U 12 (one time injection) weeks	Chankrachang*, 2011[8]* Low	0/43	1/21	0.2 (0.0 to 4.0)	0.054	-0.04 (-0.10 to 0.02)	0.169
Pyrexia	120U 12 (one time injection) weeks	Chrankrachang, 2011[8] Low	0/43	1/21	0.2 (0.0 to 4.0)	0.054	-0.04 (-0.10 to 0.02)	0.169
Pyrexia	All doses	Pooled	22/418	12/169	0.5 (0.1 to 1.3)	1	-0.04 (-0.09 to 0.01)	1

Bold = significant differences at 95% confidence limit when 95% CI of relative measure of the association estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0; CrI = credible intervals; * trials of abobotulinumtoxinA

Appendix Table D118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Edema	Chankrachang*, 2011[8]* Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Eyelid edema	Elkind, 2006[7] Low	25 vs. 7.5	0/101	1/105	0.3 (0.0 to 8.4)	-0.01 (-0.04 to 0.02)
Eyelid edema	Elkind, 2006[7] **Low**	**50 vs. 25**	**7/106**	**0/101**	**14.3 (0.8 to 247.2)**	**0.07 (0.02 to 0.12)**
Eyelid edema	Elkind, 2006[7] **Low**	**50 vs. 7.5**	**7/106**	**1/105**	**6.9 (0.9 to 55.4)**	**0.06 (0.01 to 0.11)**
Eyelid edema	Relja, 2007[17] Low	150 vs. 75	0/125	2/123	0.2 (0.0 to 4.1)	-0.02 (-0.04 to 0.01)
Eyelid edema	Relja, 2007[17] Low	225 vs. 150	3/129	0/125	6.8 (0.4 to 130.0)	0.02 (-0.01 to 0.05)
Eyelid edema	Relja, 2007[17] Low	225 vs. 75	3/129	2/123	1.4 (0.2 to 8.4)	0.01 (-0.03 to 0.04)
Eyelid edema	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Rash	Relja, 2007[17] Low	150 vs. 75	0/125	3/123	0.1 (0.0 to 2.7)	-0.02 (-0.06 to 0.01)
Rash	Relja, 2007[17] Low	225 vs. 150	1/129	0/125	2.9 (0.1 to 70.7)	0.01 (-0.01 to 0.03)
Rash	Relja, 2007[17] Low	225 vs. 75	1/129	3/123	0.3 (0.0 to 3.0)	-0.02 (-0.05 to 0.01)
Adverse effects	Saper, 2007[4] Low	9 vs. 6	11/49	8/45	1.3 (0.6 to 2.9)	0.05 (-0.11 to 0.21)
Adverse effects	Saper, 2007[4] Low	10 vs. 6	9/44	8/45	1.2 (0.5 to 2.7)	0.03 (-0.14 to 0.19)
Adverse effects	Saper, 2007[4] Low	10 vs. 9	9/44	11/49	0.9 (0.4 to 2.0)	-0.02 (-0.19 to 0.15)
Adverse effects	Saper, 2007[4] Low	25 vs. 10	17/49	9/44	1.7 (0.8 to 3.4)	0.14 (-0.04 to 0.32)
Adverse effects	Saper, 2007[4] **Low**	**25 vs. 6**	**17/49**	**8/45**	**2.0 (0.9 to 4.1)**	**0.17 (0.00 to 0.34)**
Adverse effects	Saper, 2007[4] Low	25 vs. 9	17/49	11/49	1.5 (0.8 to 3.0)	0.12 (-0.05 to 0.30)
Adverse effects	Elkind, 2006[7] Low	25 vs. 7.5	47/101	52/105	0.9 (0.7 to 1.2)	-0.03 (-0.17 to 0.11)
Adverse effects	Elkind, 2006[7] Low	50 vs. 25	60/106	47/101	1.2 (0.9 to 1.6)	0.10 (-0.03 to 0.24)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Adverse effects	Elkind, 2006[7] Low	50 vs. 7.5	60/106	52/105	1.1 (0.9 to 1.5)	0.07 (-0.06 to 0.21)
Adverse effects	Relja, 2007[17] Low	150 vs. 75	79/125	77/123	1.0 (0.8 to 1.2)	0.01 (-0.11 to 0.13)
Adverse effects	Silberstein, 2005[11] Low	150 vs. 75	92/168	97/174	1.0 (0.8 to 1.2)	-0.01 (-0.12 to 0.10)
Adverse effects	**Petri*, 2009[9] High**	**210 vs. 80**	**12/32**	**4/32**	**3.0 (1.1 to 8.3)**	**0.25 (0.05 to 0.45)**
Adverse effects	Relja, 2007[17] Low	225 vs. 150	87/129	79/125	1.1 (0.9 to 1.3)	0.04 (-0.07 to 0.16)
Adverse effects	Relja, 2007[17] Low	225 vs. 75	87/129	77/123	1.1 (0.9 to 1.3)	0.05 (-0.07 to 0.17)
Adverse effects	Silberstein, 2005[11] **Low**	**225 vs. 150**	**119/182**	**92/168**	**1.2 (1.0 to 1.4)**	**0.11 (0.00 to 0.21)**
Adverse effects	Silberstein, 2005[11] **Low**	**225 vs. 75**	**119/182**	**97/174**	**1.2 (1.0 to 1.4)**	**0.10 (0.00 to 0.20)**
Adverse effects	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	139/180	135/173	1.0 (0.9 to 1.1)	-0.01 (-0.10 to 0.08)
Mastication disorder	Chankrachang*, 2011[8] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Menorrhagia	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Bronchitis	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	10/180	6/173	1.6 (0.6 to 4.3)	0.02 (-0.02 to 0.06)
Flu syndrome	Elkind, 2006[7] Low	25 vs. 7.5	4/101	11/105	0.4 (0.1 to 1.1)	-0.07 (-0.13 to 0.00)
Flu syndrome	Elkind, 2006[7] Low	50 vs. 25	7/106	4/101	1.7 (0.5 to 5.5)	0.03 (-0.03 to 0.09)
Flu syndrome	Elkind, 2006[7] Low	50 vs. 7.5	7/106	11/105	0.6 (0.3 to 1.6)	-0.04 (-0.11 to 0.04)
Flu syndrome	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	14/180	12/173	1.1 (0.5 to 2.4)	0.01 (-0.05 to 0.06)
Herpes zoster	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Infection	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	15/180	20/173	0.7 (0.4 to 1.4)	-0.03 (-0.09 to 0.03)
Respiratory infection	Elkind, 2006[7] Low	25 vs. 7.5	10/101	12/105	0.9 (0.4 to 1.9)	-0.02 (-0.10 to 0.07)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Respiratory infection	Elkind, 2006[7] Low	50 vs. 25	11/106	10/101	1.0 (0.5 to 2.4)	0.00 (-0.08 to 0.09)
Respiratory infection	Elkind, 2006[7] Low	50 vs. 7.5	11/106	12/105	0.9 (0.4 to 2.0)	-0.01 (-0.09 to 0.07)
Respiratory infection	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	12/180	14/173	0.8 (0.4 to 1.7)	-0.01 (-0.07 to 0.04)
Sinus infection	Elkind, 2006[7] Low	25 vs. 7.5	7/101	4/105	1.8 (0.5 to 6.0)	0.03 (-0.03 to 0.09)
Sinus infection	Elkind, 2006[7] Low	50 vs. 25	4/106	7/101	0.5 (0.2 to 1.8)	-0.03 (-0.09 to 0.03)
Sinus infection	Elkind, 2006[7] Low	50 vs. 7.5	4/106	4/105	1.0 (0.3 to 3.9)	0.00 (-0.05 to 0.05)
Sinus infection	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	15/180	16/173	0.9 (0.5 to 1.8)	-0.01 (-0.07 to 0.05)
Injection site hemorrhage	Relja, 2007[17] Low	150 vs. 75	2/125	3/123	0.7 (0.1 to 3.9)	-0.01 (-0.04 to 0.03)
Injection site hemorrhage	Relja, 2007[17] Low	225 vs. 150	0/129	2/125	0.2 (0.0 to 4.0)	-0.02 (-0.04 to 0.01)
Injection site hemorrhage	Relja, 2007[17] Low	225 vs. 75	0/129	3/123	0.1 (0.0 to 2.6)	-0.02 (-0.06 to 0.01)
Injection site pain	Relja, 2007[17] Low	150 vs. 75	9/125	4/123	2.2 (0.7 to 7.0)	0.04 (-0.02 to 0.09)
Injection site pain	Relja, 2007[17] Low	225 vs. 150	3/129	9/125	0.3 (0.1 to 1.2)	-0.05 (-0.10 to 0.00)
Injection site pain	Relja, 2007[17] Low	225 vs. 75	3/129	4/123	0.7 (0.2 to 3.1)	-0.01 (-0.05 to 0.03)
Injection site pain	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Injection site weakness	Silberstein, 2000[6] Medium	75 vs. 25	5/40	4/42	1.3 (0.4 to 4.5)	0.03 (-0.11 to 0.17)
Injection-site pain	Silberstein, 2005[11] Low	150 vs. 75	10/168	8/174	1.3 (0.5 to 3.2)	0.01 (-0.03 to 0.06)
Injection-site pain	Silberstein, 2005[11] Low	225 vs. 150	17/182	10/168	1.6 (0.7 to 3.3)	0.03 (-0.02 to 0.09)
Injection-site pain	Silberstein, 2005[11] Low	225 vs. 75	17/182	8/174	2.0 (0.9 to 4.6)	0.05 (-0.01 to 0.10)
Injection-site stinging	Silberstein, 2005[11] Low	150 vs. 75	5/168	2/174	2.6 (0.5 to 13.2)	0.02 (-0.01 to 0.05)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Injection-site stinging	Silberstein, 2005[11] Low	225 vs. 150	3/182	5/168	0.6 (0.1 to 2.3)	-0.01 (-0.04 to 0.02)
Injection-site stinging	Silberstein, 2005[11] Low	225 vs. 75	3/182	2/174	1.4 (0.2 to 8.5)	0.00 (-0.02 to 0.03)
Pyrexia	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Blepharoptosis	Saper, 2007[4] Low	9 vs. 6	0/49	1/45	0.3 (0.0 to 7.3)	-0.02 (-0.08 to 0.04)
Blepharoptosis	Saper, 2007[4] Low	10 vs. 6	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Blepharoptosis	Saper, 2007[4] Low	10 vs. 9	0/44	0/49	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Blepharoptosis	Saper, 2007[4] Low	25 vs. 10	4/49	0/44	8.1 (0.4 to 146.3)	0.08 (0.00 to 0.17)
Blepharoptosis	Saper, 2007[4] Low	25 vs. 6	4/49	1/45	3.7 (0.4 to 31.7)	0.06 (-0.03 to 0.15)
Blepharoptosis	Saper, 2007[4] Low	25 vs. 9	4/49	0/49	9.0 (0.5 to 162.8)	0.08 (0.00 to 0.17)
Blepharoptosis	Elkind, 2006[7] Low	25 vs. 7.5	5/101	2/105	2.6 (0.5 to 13.1)	0.03 (-0.02 to 0.08)
Blepharoptosis	Elkind, 2006[7] Low	50 vs. 25	8/106	5/101	1.5 (0.5 to 4.5)	0.03 (-0.04 to 0.09)
Blepharoptosis	Elkind, 2006[7]18329 Low	50 vs. 7.5	8/106	2/105	4.0 (0.9 to 18.2)	0.06 (0.00 to 0.11)
Blepharoptosis	Silberstein, 2000[6] Medium	75 vs. 25	7/40	6/42	1.2 (0.5 to 3.3)	0.03 (-0.13 to 0.19)
Blepharoptosis	**Relja, 2007[17] Low**	**150 vs. 75**	**12/125**	**3/123**	**3.9 (1.1 to 13.6)**	**0.07 (0.01 to 0.13)**
Blepharoptosis	Silberstein, 2005[11] Low	150 vs. 75	7/168	6/174	1.2 (0.4 to 3.5)	0.01 (-0.03 to 0.05)
Blepharoptosis	Relja, 2007[17] Low	225 vs. 150	18/129	12/125	1.5 (0.7 to 2.9)	0.04 (-0.04 to 0.12)
Blepharoptosis	**Relja, 2007[17] Low**	**225 vs. 75**	**18/129**	**3/123**	**5.7 (1.7 to 18.9)**	**0.12 (0.05 to 0.18)**
Blepharoptosis	Silberstein, 2005[11] Low	225 vs. 150	12/182	7/168	1.6 (0.6 to 3.9)	0.02 (-0.02 to 0.07)
Blepharoptosis	Silberstein, 2005[11] Low	225 vs. 75	12/182	6/174	1.9 (0.7 to 5.0)	0.03 (-0.01 to 0.08)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Blepharoptosis	Chankrachang*, 2011[8] Risk of bias Low	240 vs. 120	2/43	0/43	5.0 (0.2 to 101.2)	0.05 (-0.03 to 0.12)
Blepharoptosis	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	16/180	7/173	2.2 (0.9 to 5.2)	0.05 (0.00 to 0.10)
Muscle tightness	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	2/43	0.2 (0.0 to 4.0)	-0.05 (-0.12 to 0.03)
Muscle weakness	Saper, 2007[4] Low	9 vs. 6	0/49	0/45	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[4] Low	10 vs. 6	0/44	0/45	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[4] Low	10 vs. 9	0/44	0/49	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Muscle weakness	Saper, 2007[4] **Low**	**25 vs. 10**	**6/49**	**0/44**	**11.7 (0.7 to 201.9)**	**0.12 (0.02 to 0.22)**
Muscle weakness	**Saper, 2007[4] Low**	**25 vs. 6**	**6/49**	**0/45**	**12.0 (0.7 to 206.4)**	**0.12 (0.02 to 0.22)**
Muscle weakness	**Saper, 2007[4] Low**	**25 vs. 9**	**6/49**	**0/49**	**13.0 (0.8 to 224.7)**	**0.12 (0.03 to 0.22)**
Muscle weakness	Relja, 2007[17] Low	150 vs. 75	35/125	30/123	1.1 (0.8 to 1.7)	0.04 (-0.07 to 0.15)
Muscle weakness	**Silberstein, 2005[11] Low**	**150 vs. 75**	**44/168**	**29/174**	**1.6 (1.0 to 2.4)**	**0.10 (0.01 to 0.18)**
Muscle weakness	Relja, 2007[17] Low	225 vs. 150	35/129	35/125	1.0 (0.7 to 1.4)	-0.01 (-0.12 to 0.10)
Muscle weakness	Relja, 2007[17] Low	225 vs. 75	35/129	30/123	1.1 (0.7 to 1.7)	0.03 (-0.08 to 0.14)
Muscle weakness	Silberstein, 2005[11] Low	225 vs. 150	56/182	44/168	1.2 (0.8 to 1.6)	0.05 (-0.05 to 0.14)
Muscle weakness	**Silberstein, 2005[11] Low**	**225 vs. 75**	**56/182**	**29/174**	**1.8 (1.2 to 2.7)**	**0.14 (0.05 to 0.23)**
Musculoskeletal stiffness	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Neck rigidity	Relja, 2007[17] Low	150 vs. 75	20/125	13/123	1.5 (0.8 to 2.9)	0.05 (-0.03 to 0.14)
Neck rigidity	Silberstein, 2005[11] Low	150 vs. 75	14/168	14/174	1.0 (0.5 to 2.1)	0.00 (-0.06 to 0.06)
Neck rigidity	Relja, 2007[17] Low	225 vs. 150	22/129	20/125	1.1 (0.6 to 1.9)	0.01 (-0.08 to 0.10)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Neck rigidity	Relja, 2007[17] Low	225 vs. 75	22/129	13/123	1.6 (0.9 to 3.1)	0.06 (-0.02 to 0.15)
Neck rigidity	**Silberstein, 2005[11] Low**	**225 vs. 150**	**27/182**	**14/168**	**1.8 (1.0 to 3.3)**	**0.07 (0.00 to 0.13)**
Neck rigidity	**Silberstein, 2005[11] Low**	**225 vs. 75**	**27/182**	**14/174**	**1.8 (1.0 to 3.4)**	**0.07 (0.00 to 0.13)**
Skin tightness	Relja, 2007[17] Low	150 vs. 75	9/125	7/123	1.3 (0.5 to 3.3)	0.02 (-0.05 to 0.08)
Skin tightness	Relja, 2007[17] Low	225 vs. 150	6/129	9/125	0.6 (0.2 to 1.8)	-0.03 (-0.08 to 0.03)
Skin tightness	Relja, 2007[17] Low	225 vs. 75	6/129	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.07 to 0.04)
Tenderness	Chankrachang*, 2011[8] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Diplopia	Silberstein, 2000[6] Medium	75 vs. 25	2/40	0/42	5.2 (0.3 to 106.0)	0.05 (-0.03 to 0.13)
Dizziness	Relja, 2007[17] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Dizziness	Relja, 2007[17] Low	225 vs. 150	2/129	3/125	0.6 (0.1 to 3.8)	-0.01 (-0.04 to 0.03)
Dizziness	Relja, 2007[17] Low	225 vs. 75	2/129	3/123	0.6 (0.1 to 3.7)	-0.01 (-0.04 to 0.03)
Dizziness	Chankrachang*, 2011[8] Low	240 vs. 120	1/43	2/43	0.5 (0.0 to 5.3)	-0.02 (-0.10 to 0.05)
Dizziness	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	9/180	2/173	4.3 (0.9 to 19.7)	0.04 (0.00 to 0.07)
Dyskinesia	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Dysphagia	Relja, 2007[17] Low	150 vs. 75	3/125	1/123	3.0 (0.3 to 28.0)	0.02 (-0.02 to 0.05)
Dysphagia	Silberstein, 2005[11] Low	150 vs. 75	5/168	3/174	1.7 (0.4 to 7.1)	0.01 (-0.02 to 0.04)
Dysphagia	Relja, 2007[17] Low	225 vs. 150	4/129	3/125	1.3 (0.3 to 5.7)	0.01 (-0.03 to 0.05)
Dysphagia	Relja, 2007[17] Low	225 vs. 75	4/129	1/123	3.8 (0.4 to 33.6)	0.02 (-0.01 to 0.06)
Dysphagia	Silberstein, 2005[11] Low	225 vs. 150	11/182	5/168	2.0 (0.7 to 5.7)	0.03 (-0.01 to 0.07)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Dysphagia	Silberstein, 2005[11] Low	225 vs. 75	11/182	3/174	3.5 (1.0 to 12.4)	0.04 (0.00 to 0.08)
Hypertonia	Relja, 2007[17] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Hypertonia	Silberstein, 2005[11] Low	150 vs. 75	15/168	13/174	1.2 (0.6 to 2.4)	0.01 (-0.04 to 0.07)
Hypertonia	Relja, 2007[17] Low	225 vs. 150	4/129	3/125	1.3 (0.3 to 5.7)	0.01 (-0.03 to 0.05)
Hypertonia	Relja, 2007[17] Low	225 vs. 75	4/129	3/123	1.3 (0.3 to 5.6)	0.01 (-0.03 to 0.05)
Hypertonia	Silberstein, 2005[11] Low	225 vs. 150	13/182	15/168	0.8 (0.4 to 1.6)	-0.02 (-0.07 to 0.04)
Hypertonia	Silberstein, 2005[11] Low	225 vs. 75	13/182	13/174	1.0 (0.5 to 2.0)	0.00 (-0.06 to 0.05)
Hypesthesia	Silberstein, 2005[11] Low	150 vs. 75	11/168	11/174	1.0 (0.5 to 2.3)	0.00 (-0.05 to 0.05)
Hypesthesia	Silberstein, 2005[11] Low	225 vs. 150	12/182	11/168	1.0 (0.5 to 2.2)	0.00 (-0.05 to 0.05)
Hypesthesia	Silberstein, 2005[11] Low	225 vs. 75	12/182	11/174	1.0 (0.5 to 2.3)	0.00 (-0.05 to 0.05)
Hypoesthesia	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Nausea	Relja, 2007[17] Low	150 vs. 75	2/125	1/123	2.0 (0.2 to 21.4)	0.01 (-0.02 to 0.03)
Nausea	Relja, 2007[17] Low	225 vs. 150	4/129	2/125	1.9 (0.4 to 10.4)	0.02 (-0.02 to 0.05)
Nausea	Relja, 2007[17] Low	225 vs. 75	4/129	1/123	3.8 (0.4 to 33.6)	0.02 (-0.01 to 0.06)
Nausea	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Paresthesia	Relja, 2007[17] Low	150 vs. 75	4/125	4/123	1.0 (0.3 to 3.8)	0.00 (-0.04 to 0.04)
Paresthesia	Relja, 2007[17] Low	225 vs. 150	6/129	4/125	1.5 (0.4 to 5.0)	0.01 (-0.03 to 0.06)
Paresthesia	Relja, 2007[17] Low	225 vs. 75	6/129	4/123	1.4 (0.4 to 4.9)	0.01 (-0.03 to 0.06)
Sedation	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Somnolence	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Trismus	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Vomiting	Chankrachang*, 2011[8] Low	240 vs. 120	1/43	0/43	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Arm pain	Relja, 2007[17] Low	150 vs. 75	6/125	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.06 to 0.05)
Arm pain	Relja, 2007[17] Low	225 vs. 150	6/129	6/125	1.0 (0.3 to 2.9)	0.00 (-0.05 to 0.05)
Arm pain	Relja, 2007[17] Low	225 vs. 75	6/129	7/123	0.8 (0.3 to 2.4)	-0.01 (-0.07 to 0.04)
Asthenia	Relja, 2007[17] Low	150 vs. 75	3/125	4/123	0.7 (0.2 to 3.2)	-0.01 (-0.05 to 0.03)
Asthenia	Silberstein, 2005[11] Low	150 vs. 75	6/168	1/174	6.2 (0.8 to 51.1)	0.03 (0.00 to 0.06)
Asthenia	Relja, 2007[17] Low	225 vs. 150	5/129	3/125	1.6 (0.4 to 6.6)	0.01 (-0.03 to 0.06)
Asthenia	Relja, 2007[17] Low	225 vs. 75	5/129	4/123	1.2 (0.3 to 4.3)	0.01 (-0.04 to 0.05)
Asthenia	Silberstein, 2005[11] Low	225 vs. 150	2/182	6/168	0.3 (0.1 to 1.5)	-0.02 (-0.06 to 0.01)
Asthenia	Silberstein, 2005[11] Low	225 vs. 75	2/182	1/174	1.9 (0.2 to 20.9)	0.01 (-0.01 to 0.02)
Back pain	Silberstein, 2005[11] Low	150 vs. 75	4/168	3/174	1.4 (0.3 to 6.1)	0.01 (-0.02 to 0.04)
Back pain	Silberstein, 2005[11] Low	225 vs. 150	6/182	4/168	1.4 (0.4 to 4.8)	0.01 (-0.03 to 0.04)
Back pain	Silberstein, 2005[11] Low	225 vs. 75	6/182	3/174	1.9 (0.5 to 7.5)	0.02 (-0.02 to 0.05)
Face pain	Relja, 2007[17] Low	150 vs. 75	6/125	4/123	1.5 (0.4 to 5.1)	0.02 (-0.03 to 0.06)
Face pain	Relja, 2007[17] Low	225 vs. 150	4/129	6/125	0.6 (0.2 to 2.2)	-0.02 (-0.06 to 0.03)
Face pain	Relja, 2007[17] Low	225 vs. 75	4/129	4/123	1.0 (0.2 to 3.7)	0.00 (-0.04 to 0.04)
Headache	Saper, 2007[4] Low	9 vs. 6	0/49	2/45	0.2 (0.0 to 3.7)	-0.04 (-0.12 to 0.03)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Headache	Saper, 2007[4] Low	10 vs. 6	1/44	2/45	0.5 (0.0 to 5.4)	-0.02 (-0.10 to 0.05)
Headache	Saper, 2007[4] Low	10 vs. 9	1/44	0/49	3.3 (0.1 to 79.8)	0.02 (-0.04 to 0.08)
Headache	Saper, 2007[4] Low	25 vs. 10	3/49	1/44	2.7 (0.3 to 25.0)	0.04 (-0.04 to 0.12)
Headache	Saper, 2007[4] Low	25 vs. 6	3/49	2/45	1.4 (0.2 to 7.9)	0.02 (-0.07 to 0.11)
Headache	Saper, 2007[4] Low	25 vs. 9	3/49	0/49	7.0 (0.4 to 132.0)	0.06 (-0.01 to 0.14)
Headache	Elkind, 2006[7] Low	25 vs. 7.5	2/101	1/105	2.1 (0.2 to 22.6)	0.01 (-0.02 to 0.04)
Headache	Elkind, 2006[7] Low	50 vs. 25	8/106	2/101	3.8 (0.8 to 17.5)	0.06 (0.00 to 0.11)
Headache	**Elkind, 2006[7] Low**	**50 vs. 7.5**	**8/106**	**1/105**	**7.9 (1.0 to 62.3)**	**0.07 (0.01 to 0.12)**
Headache	Relja, 2007[17] Low	150 vs. 75	5/125	4/123	1.2 (0.3 to 4.5)	0.01 (-0.04 to 0.05)
Headache	Silberstein, 2005[11] Low	150 vs. 75	14/168	7/174	2.1 (0.9 to 5.0)	0.04 (-0.01 to 0.09)
Headache	Relja, 2007[17] Low	225 vs. 150	2/129	5/125	0.4 (0.1 to 2.0)	-0.02 (-0.06 to 0.02)
Headache	Relja, 2007[17] Low	225 vs. 75	2/129	4/123	0.5 (0.1 to 2.6)	-0.02 (-0.05 to 0.02)
Headache	Silberstein, 2005[11] Low	225 vs. 150	15/182	14/168	1.0 (0.5 to 2.0)	0.00 (-0.06 to 0.06)
Headache	Silberstein, 2005[11] Low	225 vs. 75	15/182	7/174	2.0 (0.9 to 4.9)	0.04 (-0.01 to 0.09)
Headache	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	0/43	0.0 (0.0 to 0.0)	0.00 (-0.04 to 0.04)
Headache	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	10/180	8/173	1.2 (0.5 to 3.0)	0.01 (-0.04 to 0.06)
Infection site pain	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	4/180	9/173	0.4 (0.1 to 1.4)	-0.03 (-0.07 to 0.01)
Malaise	Relja, 2007[17] Low	150 vs. 75	0/125	0/123	0.0 (0.0 to 0.0)	0.00 (-0.02 to 0.02)
Malaise	Relja, 2007[17] Low	225 vs. 150	4/129	0/125	8.7 (0.5 to 160.4)	0.03 (0.00 to 0.06)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Malaise	Relja, 2007[17] Low	225 vs. 75	4/129	0/123	8.6 (0.5 to 157.8)	0.03 (0.00 to 0.06)
Migraine	Relja, 2007[17] Low	150 vs. 75	3/125	2/123	1.5 (0.3 to 8.7)	0.01 (-0.03 to 0.04)
Migraine	Silberstein, 2005[11] Low	150 vs. 75	5/168	2/174	2.6 (0.5 to 13.2)	0.02 (-0.01 to 0.05)
Migraine	Relja, 2007[17] Low	225 vs. 150	1/129	3/125	0.3 (0.0 to 3.1)	-0.02 (-0.05 to 0.01)
Migraine	Relja, 2007[17] Low	225 vs. 75	1/129	2/123	0.5 (0.0 to 5.2)	-0.01 (-0.04 to 0.02)
Migraine	Silberstein, 2005[11] Low	225 vs. 150	0/182	5/168	0.1 (0.0 to 1.5)	-0.03 (-0.06 to 0.00)
Migraine	Silberstein, 2005[11] Low	225 vs. 75	0/182	2/174	0.2 (0.0 to 4.0)	-0.01 (-0.03 to 0.01)
Myalgia	Relja, 2007[17] Low	150 vs. 75	5/125	7/123	0.7 (0.2 to 2.2)	-0.02 (-0.07 to 0.04)
Myalgia	Relja, 2007[17] Low	225 vs. 150	10/129	5/125	1.9 (0.7 to 5.5)	0.04 (-0.02 to 0.10)
Myalgia	Relja, 2007[17] Low	225 vs. 75	10/129	7/123	1.4 (0.5 to 3.5)	0.02 (-0.04 to 0.08)
Neck pain	Relja, 2007[17] Low	150 vs. 75	24/125	22/123	1.1 (0.6 to 1.8)	0.01 (-0.08 to 0.11)
Neck pain	Silberstein, 2005[11] Low	150 vs. 75	37/168	30/174	1.3 (0.8 to 2.0)	0.05 (-0.04 to 0.13)
Neck pain	Relja, 2007[17] Low	225 vs. 150	30/129	24/125	1.2 (0.8 to 2.0)	0.04 (-0.06 to 0.14)
Neck pain	Relja, 2007[17] Low	225 vs. 75	30/129	22/123	1.3 (0.8 to 2.1)	0.05 (-0.05 to 0.15)
Neck pain	Silberstein, 2005[11] Low	225 vs. 150	41/182	37/168	1.0 (0.7 to 1.5)	0.01 (-0.08 to 0.09)
Neck pain	Silberstein, 2005[11] Low	225 vs. 75	41/182	30/174	1.3 (0.9 to 2.0)	0.05 (-0.03 to 0.14)
Neck pain	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	2/43	0.2 (0.0 to 4.0)	-0.05 (-0.12 to 0.03)
Pain	Relja, 2007[17] Low	150 vs. 75	3/125	3/123	1.0 (0.2 to 4.8)	0.00 (-0.04 to 0.04)
Pain	Relja, 2007[17] Low	225 vs. 150	5/129	3/125	1.6 (0.4 to 6.6)	0.01 (-0.03 to 0.06)

Appendix Table 118. Dose response adverse effects with onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effect	Reference Risk of Bias	Dose of Drug, Units	Events/ Randomized Larger Dose	Events/ Randomized Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Pain	Relja, 2007[17] Low	225 vs. 75	5/129	3/123	1.6 (0.4 to 6.5)	0.01 (-0.03 to 0.06)
Pain	Elkind, 2006[7] Low	7.5 or 50 vs. 7.5 or 25	14/180	13/173	1.0 (0.5 to 2.1)	0.00 (-0.05 to 0.06)
Radicular pain	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Shoulder / arm pain	Silberstein, 2005[11] Low	150 vs. 75	11/168	8/174	1.4 (0.6 to 3.5)	0.02 (-0.03 to 0.07)
Shoulder / arm pain	Silberstein, 2005[11] Low	225 vs. 150	12/182	11/168	1.0 (0.5 to 2.2)	0.00 (-0.05 to 0.05)
Shoulder / arm pain	Silberstein, 2005[11] Low	225 vs. 75	12/182	8/174	1.4 (0.6 to 3.4)	0.02 (-0.03 to 0.07)
Tension headache	Chankrachang*, 2011[8] Low	240 vs. 120	0/43	1/43	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)

CI = confidence interval
Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
* trials of abobotulinumtoxinA

Appendix Table D119. Randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Country where Study was Conducted	Total Sample [Number Analyzed] % Females	Age	Definition of Migraine	Presence of Aura	Duration of Migraine	Migraine Frequency/ Month	Baseline Comorbidity
Storey, 2001[18]	Not reported	40 [Not reported] 97.5% female	Mean 38.2 years	International Headache Society (IHS) criteria	Not reported	Not reported	4.7	Not reported
Edwards, 2003[19]	Previously reported	70 [70] 97.1% female	Mean 41.1 years	International Headache Society criteria	Not reported	Not reported	4.5	Not reported
Silvestrini, 2003[20]	Italy	28 [28] 64.3% female	Mean 43.5 years	International Headache Society criteria	All patients had a history of migraine without aura attacks as inclusion criterion	3 years	20	Not reported
Brandes, 2004[22]	North America	483 [468] 86.8% female	Mean 38.9 years	International Headache Society criteria	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2004[23]	USA	487 [469] 89.1% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported
Mei, 2004[24]	Italy	115 [72] 54.2% female	Mean 39.2 years	International Headache Society (1988) criteria	Patients with migraine without aura, n (%): Topiramate: 27 (77), Placebo: 31 (84)	Not reported	5.5	Not reported
Bussone, 2005[25]	Not reported (Pooled analysis)	758 [756] 84.3% female	Mean 39.8 years	International Headache Society criteria	Not reported	Not reported	5.4	Not reported
Silberstein, 2006[27]	USA	469 (ITT population). Number randomized not given [469] 88.7% female	Mean 40.4 years	International Headache Society criteria	Not reported	Not reported	5.5	Not reported

Appendix Table 119. Randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Country where Study was Conducted	Total Sample [Number Analyzed] % Females	Age	Definition of Migraine	Presence of Aura	Duration of Migraine	Migraine Frequency/ Month	Baseline Comorbidity
Mei, 2006[28]	Italy	50 [35] 68.6% female	Mean 45.9 years	International Classification of Headache Disorders 2nd Edition	Not reported	4.97 years	Not reported	Not reported
Silberstein, 2006[29]	USA	213 [Variable] 85.8% female	Mean 40.5 years	International Headache Society criteria	75 subjects had migraine with aura	Not reported	4.9	Not reported
Brandes, 2006[30]	USA	483 [468] 86.8% female	Mean 38.9 years	International Headache Society criteria for migraine with or without aura	Not reported	At least 6 months	5.5	Not reported
Silberstein, 2007[31]	USA	328 [Variable] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration:9.2 years; Age at onset (years): 19.7	Not reported	Not reported
Diener, 2007[34]	Not reported	59 [59] 74.5% female	Mean 46 years	Second edition of The International Classification of Headache Disorders criteria	Not reported	At least 1 year	Not reported	Beck Depression Inventory, mean (SD): Placebo: 13.4 (8.8), Topiramate: 9.0 (7.0)
Lainez, 2007[35]	Not reported	774 [758] 84.4% female	Mean 39.9 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported
Diener, 2007[38]	21 countries in Europe	818 in open-label phase and 514 in the double-blind phase [Not reported] 89.0% female	Mean 40·1 years	International Headache Society criteria	Not reported	Not reported	8.7	Not reported
Adelman, 2008[40]	USA, Australia, Canada, Denmark, Finland,	1580 [1580] 85.0% female	Mean 40.1 years	International Headache Society criteria	Not reported	Not reported	Not reported	Not reported

Appendix Table 119. Randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Country where Study was Conducted	Total Sample [Number Analyzed] % Females	Age	Definition of Migraine	Presence of Aura	Duration of Migraine	Migraine Frequency/ Month	Baseline Comorbidity
	France, Germany, Italy, Korea, the Netherlands, South Africa, Spain, Sweden, Taiwan, and the United Kingdom							
Silberstein, 2009[41]	USA	328 [321] 85.3% female	Mean 38.2 years	International Headache Society 1.1 or 1.2	Not reported	Duration:9.2 years; Age at onset (years): 19.7	Not reported	Not reported
Lipton, 2011[42]	Not reported	385 [Variable] 10.9% female	Mean 40.3 years	International Headache Society criteria 1.1,1.2	Not reported	Age at migraine onset (years): 20.3	Not reported	Not reported

SD = Standard deviation

Appendix Table D120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
Storey, 2001[18]	Industry	Yes	Yes	Not reported	Not applicable
Edwards, 2003[19]	Industry	Yes	Yes	Yes	Ms. Potter is on the Speakers' Bureau for biogen, GlaxoSmithKline and Ortho-McNeil Pharmaceutical, Inc, and has received funding from Biogen, Ortho-McNeil Pharmaceutical, Inc, Pfizer Inc, Wyeth Pharmaceuticals for previous research
Silvestrini, 2003[20]	Not reported	Yes	Yes	Not reported	Not applicable
Brandes, 2004[22]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, Allergan, UCB Pharma, Johnson & Johnson, AstraZeneca, Pfizer, Bristol Myers-Squibb, Winston Laboratories, Forest Laboratories, Sanofi-Synthelabo, and Elan Pharmaceuticals; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Merck, Allergan, Pfizer, Pharmacia, Ortho-McNeil, and UCB Pharma; has served as a consultant to Merck, GlaxoSmithKline, Pfizer, AstraZeneca, Allergan, and Ortho-McNeil; and has received educational funding from GlaxoSmithKline. Dr Saper has received research grants from GlaxoSmithKline, AstraZeneca, Merck, Abbott, Allergan, Elan, Pfizer, Ortho-McNeil, and Novartis; has served on advisory boards or as a consultant for AstraZeneca, GlaxoSmithKline, Allergan, Ortho-McNeil, and Medtronic; and has served on the speakers bureau for GlaxoSmithKline, Merck, AstraZeneca, Ortho-McNeil, Pfizer, and Xcel. Dr Diamond has served as a speaker, consultant, or both or has conducted research for AstraZeneca, Bristol-Myers Squibb, Ortho- McNeil, Elan, GlaxoSmithKline, Merck, and Pfizer. Dr Couch has participated in research for, been an advisory board member of, and served as a speaker for Ortho-McNeil.
Silberstein, 2004[23]	Industry	Yes	Yes	Yes	Silberstein is on the advisory panel of, speakers bureau of, or serves as a consultant for Abbott Laboratories, Allergan, Inc, AstraZeneca, Elan Pharmaceutical Research Corp, Eli Lilly, Ortho-McNeil Pharmaceutical, Merck & Co, and GlaxoSmithKline; receives research support from Allergan, Inc, AstraZeneca, Eli Lilly, GlaxoSmithKline, Janssen Pharmaceutical, Merck & Co, Ortho-McNeil Pharmaceutical, Pfizer, Inc, UCB Pharma, and Vernalis; and has received educational grants from Abbott Laboratories, Allergan, Inc, AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Merck & Co, Ortho-McNeil Pharmaceutical, and Parke-Davis. Drs Neto and Jacobs and Ms Schmitt hold shares in Johnson & Johnson Pharmaceutical Research and Development, LLC, a subsidiary of Johnson & Johnson Corporation.
Mei, 2004[24]	Not reported	Yes	Yes	Not reported	Not applicable

Appendix Table 120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
Bussone, 2005[25]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[27]	Industry	Yes	Yes	Yes	George Papadopoulos is from Johnson and Johnson Pharmaceutical Services, LLC, Raritan, NJ, USA and Steven Greenberg from Ortho-McNeil Neurologies, Titusville, NJ, USA. Personnel of Pharmaceutical Research and Development , Ortho-McNeil Neurologics, Inc, Titusville, New Jersey, and Phase Five Communications, New York, New York, contributed to the preparation of the manuscript
Mei, 2006[28]	Not reported	Yes	Yes	Not reported	Not applicable
Silberstein, 2006[29]	Industry	Yes	Yes	Not reported	Not applicable
Brandes, 2006[30]	Industry	Yes	Yes	Yes	Dr. Brandes has received grants or research support from Merck & Co, Inc, GlaxoSmithKline, UCB Pharma, Allergan Inc, Johnson & Johnson, Astra-Zeneca Pharmaceuticals LP, Pfizer Inc, Bristol-Meyers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Inc, Novartis, Endo Pharmaceuticals, Pozen, Vernalis, Ortho-McNeil, and Advanced Bionics; has served on the speaker's bureau for GlaxoSmith-Kline, AstraZeneca Pharmaceuticals LP, Pfizer Inc, Merck & Co, Inc, Ortho-McNeil, Allergan Inc, MedPointe Pharmaceuticals, Endo Pharmaceuticals, UCB Pharma; has served as a consultant to Merck & Co, Inc, GlaxoSmithKline, Pfizer Inc, AstraZeneca Pharmaceuticals LP, Allergan Inc, Ortho-McNeil, and Aradigm Corp; and has received an educational grant from GlaxoSmithKline. Dr Kudrow has been on a speaker's bureau of GlaxoSmithKline and Ortho-McNeil and has received grant and research support from Ortho-McNeil, GlaxoSmithKline, Pozen, Merck & Co, Inc, and Eisai Inc. Dr Fairclough received financial support as a consultant to perform analyses of the data in this study. Drs Rupnow and Greenberg are fulltime employees of Johnson & Johnson. Dr Rothrock has served as a paid consultant to Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Pozen, and Allergan Inc; has received research support from those companies and from Abbott Laboratories, Elan Corporation, Esai Inc, and AstraZeneca Pharmaceuticals LP; and has received honoraria for lecturing from Ortho-McNeil, GlaxoSmithKline, Merck & Co, Inc, Pfizer Inc, Elan Corporation, and Endo Pharmaceuticals.
Silberstein, 2007[31]	Industry	Yes	Yes	Yes	Dr. Silberstein has received personal compensation for activities with: GlaxoSmith-Kline, Inc., Johnson & Johnson, Merck & Co., Inc., UCB Pharma, AstraZeneca Pharmaceuticals, Inc., Pfizer, Inc., Allergan, Inc., Pozen, Inc., Abbott Laboratories, Inc., Eli Lilly & Company, NPS, and Xcel

Appendix Table 120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
					Pharmaceuticals; has received personal compensation in an editorial capacity for CurrentPain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Inc., Johnson & Johnson, Merck&Co., Inc., Pfizer, Inc., Allergan, Inc., and Abbott Laboratories, Inc. Dr. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan,Inc., Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil, Pfizer, Pozen, among other companies. Dr. Dodick has received personal compensation for activities with Allergan, Inc., GlaxoSmith-Kline, Inc., Pfizer, Inc., Endo Pharmaceuticals, Ortho-McNeil Pharmaceutical, Inc., Merck & Co., Inc., Medtronic, Neuralieve; has received personal compensation in an editorial capacity for Headache Currents; and has received research support from St. Jude, Allergan, Inc., Medtronic, Inc., National Institutes of Health, Mayo Clinic College of Medicine, and Advanced Bionics. Dr. Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer, Inc., and GlaxoSmithKline, Inc., and has received research support from Alzyer, AstraZeneca Pharmaceuticals, Inc., GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Precision, Division of Boston Scientific, Solvay S.A., and Vernalis. Dr. Ramadan has received personal compensation for activities with GlaxoSmithKline, Inc., Ortho- McNeil Neurologics, Inc., Eli Lilly & Company, Eisai, Inc., AstraZeneca Pharmaceuticals, Bristol-Myers Squibb Company, Pfizer, Inc., Merck & Co., Inc., Aradign Corp., Boehringer Ingelheim Pharmaceuticals and Map Pharmaceuticals; has received personal compensation in an editorial capacity for Web Alert; and has received research support from Ortho-McNeil Neurologics, Eli Lilly&Company, Pfizer, Inc., and the National Headache Ambassador Program. Dr. Mathew has received personal compensation for activities with Eisai. Dr. Brandes has received grants or research support from Merck, GlaxoSmithKline, UCB Pharma, Allergan, Johnson & Johnson, AstraZeneca, Pfizer, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan Pharmaceuticals, Novartis, Endo, Pozen, Inc., Vernalis, Ortho-McNeil, Advanced Bionics; has served on the speakers bureau for GlaxoSmithKline, AstraZeneca, Pfizer, Merck, Ortho-McNeil, Allergan, MedPointe Pharmaceuticals, Endo, UCB Pharma; has served as a consultant to Merck, GlaxoSmith-Kline, Pfizer, AstraZeneca, Allergan, Ortho-McNeil, Aradigm Corporation; and has received educational funding from GlaxoSmithKline. Dr. Bigal has received personal compensation for activities from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil,

Appendix Table 120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
					UCB, AstraZeneca, Pfizer, Inc., and Advance PCS and has received research support from Allergan, Boehringer Ingelheim, GlaxoSmithKline, Merck, Ortho-McNeil, Pfizer, UCB, AstraZeneca, and Advance PCS. Dr. Saper has received honoraria for speaking from GlaxoSmithKline, Merck & Co., Inc., Abbott Laboratories, Inc., Elan Corporation, AstraZeneca Pharmaceuticals, Pfizer, Inc., Ortho-McNeil Pharmaceuticals, Bristol-Myers Squibb, Medtronic, Inc., Endo Pharmaceuticals, Advanced Bionics, Pozen, Inc., and Penwest Pharmaceuticals Co; has received personal compensation in an editorial capacity for Pain Watch and Migraine Monitor; holds stock in Pozen, Inc.; and has received research support from Novartis, Ortho-McNeil Pharmaceuticals, Merck & Co., Inc., GlaxoSmithKline, Allergan, Inc., Eisai, Inc., AstraZeneca Pharmaceuticals, Abbott, Advanced Bionics, Medtronic, Renovis, and Pozen, Inc.Dr. Ascher is an employee of Ortho-McNeil Janssen Scientific Affairs, LLC. Dr. Jordan is an employee of PriCara, a Unit of Ortho-McNeil, Inc. Drs. Greenberg and Joseph Hulihan are employees of Ortho-McNeil Neurologics.
Diener, 2007[34]	Industry	Not reported	Not reported	Yes	JC Van Oene, M Lahaye and S Schwalen are employees of Janssen-Cilag
Lainez, 2007[35]	Not reported	Yes	Yes	Yes	Miguel JA La´ inez has received personal compensation or research support from activities with Allergan, Inc., Almirall SA, GlaxoSmithKline, Inc Jansen Cilag, Inc., Menarini, Merck & Co., Inc, Medtronic and Pfizer Inc. Frederick Freitag has received personal compensation for activities with Allergan, Inc., AstraZeneca Pharmaceuticals,., Ortho-McNeil Pharmaceuticals, Inc., Valeant Pharmaceuticals International, Pfizer Inc, and GlaxoSmithKline, Inc. Dr. Freitag has received research support from Alzyer, AstraZeneca Pharmaceuticals, GlaxoSmithKline, Inc., Merck & Co., Inc., Ortho-McNeil Pharmaceuticals, Inc., Advanced Bionics, Solvay S.A., and Vernalis. Joop Pfeil is a paid consultant for Janssen Pharmaceutical/J & J, Novartis, Sanofi-Aventis, Pfizer, Schering-Plough, Numico, Vitatron, Actelion Pharmaceuticals and Sankyo. S. Ascher is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. W.H. Olson is a full-time employee of Ortho-McNeil Janssen Pharmaceutical. S. Schwalen is a full-time employee of Janssen-Cilag GmbH.
Diener, 2007[38]	Industry	Yes	Yes	Yes	Hans-Christoph Diener, Reto Agosti, Gianni Allais, Gennaro Bussone, Brendan Davies, Michel Lanteri-Minet, Mustafa Ertas, Uwe Reuter, Margarita Sanchez Del Rio, and Jean Schoenen have participated in clinical trials and advisory boards for Janssen-Cilag. Paul Bergmans, Susanne Schwalen, Joop van Oene are employees of Janssen-Cilag EMEA (Europe, Middle East, and Africa). Hans-Chirstoph Diener has received honoraria from Addex Pharmaceuticals, Allergan, Almirall, AstraZeneca, Bayer Vital, Berlin Chemie, CoLucid Pharmaceuticals, Böhringer Ingelheim, Bristol-Myers Squibb,

Appendix Table 120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
					GlaxoSmithKline, Grünenthal, Janssen-Cilag, Eli Lilly, F Hoffmann-La Roche, 3M Medica, Merck Sharp and Dohme, Novartis Pharmaceuticals, Johnson and Johnson, Pierre Fabre, Pfizer, Schaper and Brümmer, Sanofi-Aventis, and Weber and Weber, and financial support for research projects from Allergan, Almirall, AstraZeneca, Bayer, GlaxoSmithKline, Janssen-Cilag, and Pfizer.
Adelman, 2008[40]	Industry	Yes	Yes	Yes	James Adelman: Clinical Trials 1998–2006 (Ortho-McNeil Pharmaceuticals), Advisory Boards (Ortho-McNeil Pharmaceuticals), Speaker (Ortho-McNeil Pharmaceuticals); Frederick Freitag: Consultant, honoraria recipient (OrthoMcNeil Pharmaceuticals and Ortho-McNeil Neurologics), research grant recipient (Johnson and Johnson Pharmaceuticals, Ortho-McNeil Pharmaceuticals, and Ortho-McNeil Neurologics); Miguel Lainez: grant/research recipient, consultant/scientific advisor, honoraria recipient (Allergan, Almirall Prodesfarma, Boehringer Ingelheim, Bristol-Myers Squibb, Elan Pharmaceuticals, GlaxoSmithKline, Janssen Cilag, Johnson and Johnson, MSD, Novartis, Pierre Fabre, and Sanofi-Synthelabo).
Silberstein, 2009[41]	Industry	Yes	Yes	Yes	Stephen Silberstein has received personal compensation for activities with: Johnson & Johnson, GlaxoSmith-Kline, Merck, UCB Pharma, AstraZeneca, Pfizer, Allergan, Pozen, Abbott Laboratories., Eli Lilly & Company, NPS, and Xcel Pharmaceuticals; has received personal compensation in an editorial capacity for Current Pain and Headache; and has received financial support for scholarly activities from GlaxoSmithKline, Johnson & Johnson, Merck, Pfizer, Allergan, and Abbott Laboratories. Richard B. Lipton has consulted for, conducted studies funded by, or received lecture honoraria from Allergan, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeill, Pfizer, and Pozen, among other companies. David W. Dodick has served as a consultant for GlaxoSmithKline, Merck, Allergan, Endo, Pfizer, Eli Lilly, Addex, Solvay, and Neuralieve and has received research support from Advanced Neurostimulation Systems, Medtronic, and St. Jude. Fred Freitag has received grants and research support from Advanced Bionics Corporation, Alzyer, AstraZeneca, CAPNIA, GlaxoSmithKline, Johnson & Johnson, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Solvay, and Vernalis Pharmaceuticals. He has served as a consultant for Allergan, AstraZeneca, CAPNIA, Endo Pharmaceuticals, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, and Valeant Pharmaceuticals International. He has served on the speaker's bureaus of AstraZeneca, GlaxoSmithKline, Merck, Ortho-McNeil Pharmaceutical, Ortho-McNeil Neurologics, Pfizer, and Valeant Pharmaceuticals International. Ninan Mathew has received personal compensation for activities involving continuing medical education and for advisory board participation from Ortho McNeil, Merck, Allergan,

Appendix Table 120. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo (continued)

Reference	Funding	Ethical Approval of Study	Consent of Participants	Conflict of Interest	Conflict of Interests-Relationship
					GlaxoSmithKline, Endo, and Valiant. Jan Brandes has received grants, research support, or served as a consultant to Merck, GlaxoSmithKline, UCB Pharma, Pfizer, Allergan, Johnson & Johnson, AstraZeneca, Bristol-Myers Squibb, Winston Laboratories, Sanofi-Aventis, Elan, Novartis, Endo, Pozen, Vernalis, Ortho-McNeil, Advanced Bionics, MedPointe, and Aradigm. Marcelo E. Bigal is a full-time employee of Merck Research Laboratories. This manuscript was written during his tenure at the Albert Einstein College of Medicine. He has received, in the past, compensation from Ortho-McNeil Pharmaceutical, AstraZeneca, GlaxoSmithKline, Merck, Allergan, MAP, NMT, and Endo, among other pharmaceutical companies. Steve Ascher, Jacqueline D. Morein, and Pamela Wright are employees of Ortho-McNeil Janssen Scientific Affairs, LLC. Steven J. Greenberg is an employee of EMD Serono Inc.
Lipton, 2011[42]	Industry	Yes	Yes	Yes	Not reported, however, David Biondi, Steven Ascher, William Olson and Joseph Hulihan were from Ortho-McNeil Janssen Scientific Affairs, USA

Appendix Table D121. Risk of bias in randomized controlled clinical trials that examined adverse effects with topiramate vs. placebo

Reference	Masking of the Treatment Status	Intention to Treat Analysis	Allocation Concealment	Adequacy of Randomization	Selective Outcome Reporting	Risk of Bias
Storey, 2001[18]	Double-blind	No	Unclear	Yes (Topiramate group had no men and higher number of patients with concurrent preventative treatment), but the differences were not significant	Unclear	Low
Edwards, 2003[19]	Double-blind	Yes	Unclear	Unclear	Unclear	Low
Silvestrini, 2003[20]	Double-blind	No	Unclear	Yes	Unclear	Low
Brandes, 2004[22]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Silberstein, 2004[23]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Mei, 2004[24]	Double-blind	No	Unclear	Unclear	Unclear	Medium
Bussone, 2005[25]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[27]	Double-blind	Yes	Unclear	Not adequate. Topiramate 200mg/day group has lower % of women and higher % of men as compared to other groups, but the differences were not significant (previously reported)	Unclear	Medium
Mei, 2006[28]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Silberstein, 2006[29]	Double-blind	Yes	Unclear	Not reported	Unclear	Medium
Brandes, 2006[30]	Double-blind	Yes	Clearly adequate	Not adequate; the % of male patients was much lower in the topiramate100mg and 200mg groups, but the difference was not significant	Unclear	Medium
Brandes, 2006[30]	Double-blind	Yes	Unclear	Yes	Unclear	Low
Diener, 2007[34]	Double-blind	Yes	Unclear	Not adequate (Mean Beck Depression Inventory scores were higher in placebo as compared to topiramate), but the differences were not significant	Unclear	Medium
Lainez, 2007[35]	Double-blind	No	Unclear	Yes	Unclear	Low
Diener, 2007[38]	Double-blind	Yes	Unclear	Yes	Unclear	Medium
Adelman, 2008[40]	Double-blind	No	Unclear	Yes	Unclear	Low
Silberstein, 2009[41]	Double-blind	Yes	Clearly adequate	Yes	Unclear	Low
Lipton, 2011[42]	Double-blind	Yes	Unclear	Yes	The study mentions the significance of the outcome: ≥50% and 75% reduction in headache days and migraine headache days, however, the results are not given	Low

Appendix Table D122. Treatment discontinuation due to adverse effects with approved drugs vs. placebo (pooled with random effects models results from randomized controlled clinical trials)

Active Drug	Author, Year	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
Topiramate	Silberstein, 2006[29]	21/140	4/73	2.7 (1.0 to 7.7)	8.11	0.10 (0.02 to 0.17)	13.26	0.16 (0.02 to 0.30)	13.19
Topiramate	Silberstein, 2007[31]	18/165	10/163	1.8 (0.8 to 3.7)	14.16	0.05 (-0.01 to 0.11)	16.09	0.09 (-0.02 to 0.20)	16.26
Topiramate	Gupta, 2007[44]	3/60	3/60	1.0 (0.2 to 4.8)	3.78	0.00 (-0.08 to 0.08)	13.39	0.00 (-0.18 to 0.18)	10.36
Topiramate	Lainez, 2007[35]	96/391	41/383	2.3 (1.6 to 3.2)	38.96	0.14 (0.09 to 0.19)	17.29	0.19 (0.12 to 0.26)	20.05
Topiramate	Lipton, 2011[42]	21/188	18/197	1.2 (0.7 to 2.2)	19.75	0.02 (-0.04 to 0.08)	16.06	0.03 (-0.07 to 0.13)	17.09
Topiramate	Mei, 2004[24]	3/58	2/57	1.5 (0.3 to 8.5)	3.03	0.02 (-0.06 to 0.09)	13.92	0.04 (-0.14 to 0.22)	10.11
Topiramate	Mei, 2006[28]	9/30	6/20	1.0 (0.4 to 2.4)	11.01	0.00 (-0.26 to 0.26)	2.59	0.00 (-0.28 to 0.28)	5.58
Topiramate	Edwards, 2003[19]	6/34	0/36	13.7 (0.8 to 235.0)	1.19	0.18 (0.04 to 0.31)	7.4	0.43 (0.20 to 0.67)	7.36
Topiramate	**Pooled**	**177/1066**	**84/989**	**1.8 (1.3 to 2.4)**	**100**	**0.06 (0.02 to 0.11)**	**100**	**0.11 (0.04 to 0.19)**	**100**
Divalproex	Mathew, 1995[45]	9/70	2/37	2.4 (0.5 to 10.4)	27.42	0.08 (-0.03 to 0.18)	36.56	0.13 (-0.07 to 0.33)	34.55
Divalproex	Freitag, 2002[46]	10/237	10/204	0.9 (0.4 to 2.2)	72.58	-0.01 (-0.08 to 0.07)	63.44	-0.01 (-0.14 to 0.12)	65.45
Divalproex	Pooled	19/307	12/241	1.2 (0.5 to 2.7)	100	0.02 (-0.05 to 0.10)	100	0.04 (-0.09 to 0.17)	100
Valproate	Hering, 1992[48]	1/32	2/32	0.5 (0.0 to 5.2)	32.86	-0.03 (-0.14 to 0.07)	51.79	-0.08 (-0.32 to 0.17)	42.88
Valproate	Jensen, 1994[49]	4/43	2/43	2.0 (0.4 to 10.4)	67.14	0.05 (-0.06 to 0.15)	48.21	0.09 (-0.12 to 0.30)	57.12
Valproate	Pooled	5/75	4/75	1.3 (0.3 to 4.9)	100	0.01 (-0.07 to 0.08)	100	0.02 (-0.14 to 0.18)	100
Propranolol	Diamond, 1976[50]	6/83	1/83	6.0 (0.7 to 48.8)	28.76	0.06 (0.00 to 0.12)	93.42	0.16 (0.01 to 0.31)	75.42
Propranolol	Pradalier, 1989[53]	9/31	5/24	1.4 (0.5 to 3.6)	71.24	0.08 (-0.15 to 0.31)	6.58	0.10 (-0.17 to 0.36)	24.58

Appendix Table D122. Treatment discontinuation due to adverse effects with approved drugs vs. placebo (pooled with random effects models results from randomized controlled clinical trials) (continued)

Active Drug	Author, Year	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
Propranolol	Pooled	15/114	6/107	2.1 (0.6 to 7.7)	100	**0.06 (0.00 to 0.12)**	**100**	**0.15 (0.01 to 0.28)**	100
Active drug	Heterogeneity statistics		Degree of freedom	P value Relative risk	I squared Relative risk	P value Absolute risk different	I squared Absolute risk difference	P value, arcsine transformed risk difference	I squared, arcsine transformed risk difference
Topiramate			7	0.291	17.60%	0.014	60.30%	0.018	58.40%
Divalproex			1	0.286	12.00%	0.224	32.30%	0.242	26.90%
Valproate			1	0.343	0.00%	0.306	4.60%	0.31	2.90%
Propranolol			1	0.214	35.30%	0.857	0.00%	0.668	0.00%

CI = confidence interval

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D123. Treatment discontinuation due to specific adverse effects with topiramate vs. placebo, pooled with random effects model results from individual randomized controlled clinical trials

Adverse Effect Leading to Treatment Discontinuation	Author, Year	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
Cognitive difficulties	Lainez, 2007[35]	28/391	8/383	3.4 (1.6 to 7.4)	56.75	0.05 (0.02 to 0.08)	49.71	0.13 (0.06 to 0.20)	40.3
Cognitive difficulties	Mei, 2004[24]	7/58	0/57	14.7 (0.9 to 252.3)	23.12	0.12 (0.03 to 0.21)	29.13	0.36 (0.17 to 0.54)	33.48
Cognitive difficulties	Mei, 2006[28]	0/30	1/20	0.2 (0.0 to 5.3)	20.13	-0.05 (-0.17 to 0.07)	21.16	-0.23 (-0.51 to 0.06)	26.21
Cognitive difficulties	Pooled	35/479	9/460	2.8 (0.5 to 15.3)	100	0.05 (-0.02 to 0.12)	100	0.11 (-0.13 to 0.35)	100
Difficulty with memory	Adelman, 2008[40]	9/514	1/202	3.5 (0.4 to 27.6)	59.83	0.01 (0.00 to 0.03)	96.19	0.05 (-0.03 to 0.13)	62.52
Difficulty with memory	Mei, 2006[28]	0/30	1/20	0.2 (0.0 to 5.3)	40.17	-0.05 (-0.17 to 0.07)	3.81	-0.23 (-0.51 to 0.06)	37.48
Difficulty with memory	Pooled	9/544	2/222	1.2 (0.1 to 16.3)	100	0.01 (-0.01 to 0.03)	100	-0.05 (-0.32 to 0.21)	100
Dizziness	Lainez, 2007[35]	8/391	6/383	1.3 (0.5 to 3.7)	69.8	0.01 (-0.01 to 0.02)	74.65	0.02 (-0.05 to 0.09)	58.46
Dizziness	Mei, 2006[28]	0/30	2/20	0.1 (0.0 to 2.7)	30.2	-0.10 (-0.25 to 0.05)	25.35	-0.32 (-0.61 to -0.04)	41.54
Dizziness	Pooled	8/421	8/403	0.7 (0.1 to 5.1)	100	-0.02 (-0.11 to 0.07)	100	-0.12 (-0.45 to 0.21)	100
Fatigue	Lainez, 2007[35]	18/391	3/383	5.9 (1.7 to 19.8)	66.18	0.04 (0.02 to 0.06)	96.3	0.13 (0.06 to 0.20)	84
Fatigue	Mei, 2006[28]	1/30	1/20	0.7 (0.0 to 10.1)	33.82	-0.02 (-0.13 to 0.10)	3.7	-0.04 (-0.33 to 0.24)	16
Fatigue	**Pooled**	**19/421**	**4/403**	**2.8 (0.4 to 21.2)**	**100**	**0.04 (0.01 to 0.06)**	**100**	**0.1 (0.1 to 0.22)**	**100**
Insomnia	Lainez, 2007[35]	13/391	4/383	3.2 (1.0 to 9.7)	66.18	0.02 (0.00 to 0.04)	83.59	0.08 (0.01 to 0.15)	60.4
Insomnia	Mei, 2006[28]	0/30	1/20	0.2 (0.0 to 5.3)	33.82	-0.05 (-0.17 to 0.07)	16.41	-0.23 (-0.51 to 0.06)	39.6
Insomnia	Pooled	13/421	5/403	1.3 (0.1 to 15.1)	100	0.01 (-0.04 to 0.06)	100	-0.04 (-0.33 to 0.25)	100
Language problems	Adelman, 2008[40]	10/514	1/202	3.9 (0.5 to 30.5)	67.97	0.02 (0.00 to 0.03)	98.27	0.07 (-0.01 to 0.15)	76.93
Language problems	Mei, 2006[28]	2/30	0/20	3.4	32.03	0.07	1.73	0.26	23.07

Appendix Table D123. Treatment discontinuation due to specific adverse effects with topiramate vs. placebo, pooled with random effects model results from individual randomized controlled clinical trials (continued)

Adverse Effect Leading to Treatment Discontinuation	Author, Year	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
				(0.2 to 67.0)		(-0.05 to 0.18)		(-0.02 to 0.54)	
Language problems	Pooled	12/544	1/222	3.7 (0.7 to 20.3)	100	0.02 (0.00 to 0.03)	100	0.12 (-0.04 to 0.27)	100
Paresthesia	Lainez, 2007[35]	31/391	3/383	10.1 (3.1 to 32.8)	74.85	0.07 (0.04 to 0.10)	85.36	0.20 (0.13 to 0.27)	75.34
Paresthesia	Mei, 2004[24]	5/58	0/57	10.8 (0.6 to 191.2)	12.56	0.09 (0.01 to 0.16)	11.18	0.30 (0.12 to 0.48)	17.11
Paresthesia	Mei, 2006[28]	4/30	0/20	6.1 (0.3 to 107.4)	12.59	0.13 (-0.01 to 0.27)	3.46	0.37 (0.09 to 0.66)	7.55
Paresthesia	**Pooled**	**40/479**	**3/460**	**9.6 (3.5 to 26.5)**	**100**	**0.08 (0.05 to 0.10)**	**100**	**0.23 (0.15 to 0.31)**	**100**
Somnolence	Adelman, 2008[40]	10/514	4/202	1.0 (0.3 to 3.1)	81.03	0.00 (-0.02 to 0.02)	86.81	0.01 (-0.08 to 0.09)	83.43
Somnolence	Mei, 2004[24]	2/58	1/57	2.0 (0.2 to 21.1)	18.97	0.02 (-0.04 to 0.08)	13.19	0.05 (-0.13 to 0.24)	16.57
Somnolence	Pooled	12/572	5/259	1.1 (0.4 to 3.2)	100	0.00 (-0.02 to 0.02)	100	0.01 (-0.06 to 0.09)	100
Taste perversion	Adelman, 2008[40]	6/514	0/202	5.1 (0.3 to 90.5)	36.48	0.01 (0.00 to 0.02)	93.08	0.11 (0.03 to 0.19)	78.03
Taste perversion	Mei, 2004[24]	1/58	0/57	2.9 (0.1 to 70.9)	29.76	0.02 (-0.03 to 0.06)	5.96	0.13 (-0.05 to 0.31)	15.5
Taste perversion	Mei, 2006[28]	2/30	0/20	3.4 (0.2 to 67.0)	33.76	0.07 (-0.05 to 0.18)	0.97	0.26 (-0.02 to 0.54)	6.47
Taste perversion	Pooled	9/602	0/279	3.8 (0.7 to 21.4)	100	0.01 (0.00 to 0.02)	100	0.12 (0.05 to 0.19)	100

Heterogeneity Statistics	Degree of Freedom	P Value Relative Risk	I Squared Relative Risk	P Value Absolute Risk Difference	I Squared Absolute Risk Difference	P Value Arcsine Transformed Risk Difference	I Squared Arcsine Transformed Risk Difference
Any cognitive symptom	2	0.15	48.10%	0.08	61.30%	0.003	83.10%
Difficulty with memory	1	0.15	51.10%	0.31	4.70%	0.07	70.40%
Dizziness	1	0.16	49.20%	0.16	49.00%	0.02	80.80%

Appendix Table D123. Treatment discontinuation due to specific adverse effects with topiramate vs. placebo, pooled with random effects model results from individual randomized controlled clinical trials (continued)

Heterogeneity Statistics	Degree of Freedom	P Value Relative Risk	I Squared Relative Risk	P Value Absolute Risk Difference	I Squared Absolute Risk Difference	P Value Arcsine Transformed Risk Difference	I Squared Arcsine Transformed Risk Difference
Fatigue	1	0.12	51%	0.40	0.00%	0.30	23%
Insomnia	1	0.12	58.50%	0.24	28.70%	0.04	76.40%
Language problems	1	0.94	0.00%	0.38	0.00%	0.21	36.40%
Paresthesia	2	0.95	0.00%	0.67	0.00%	0.33	11.00%
Somnolence	1	0.61	0.00%	0.59	0.00%	0.63	0.00%
Taste perversion	2	0.97	0.00%	0.64	0.00%	0.59	0.00%

Appendix Table D124. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults[40]

Outcome, Daily Dose	Events/Randomized with Drug [Placebo]	Rate % with Drug [Placebo]	Peto Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm 1 Person (95% CI) Attributable Events per 1000 Treated (95% CI)
Abdominal pain leading to withdrawal 50mg/day	5/235 [1/92]	2.1 [0.9]	1.8 (0.3 to 10.7)	0.01 (-0.02 to 0.04)	NS
Abdominal pain leading to withdrawal 100mg/day	3/386 [1/151]	0.8 [0.9]	1.2 (0.1 to 10.4)	0.00 (-0.01 to 0.02)	NS
Abdominal pain leading to withdrawal 200mg/day	12/514 [2/202]	2.3 [0.9]	2.0 (0.6 to 6.5)	0.01 (-0.01 to 0.03)	NS
Abnormal vision leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.0]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	NS
Abnormal vision leading to withdrawal 100 mg/day	3/386 [0/151]	0.8 [0.0]	4.0 (0.3 to 50.3)	0.01 (-0.01 to 0.02)	NS
Abnormal vision leading to withdrawal 200mg/day	5/514 [0/202]	1.0 [0.0]	4.1 (0.6 to 28.6)	0.01 (0.00 to 0.02)	NS
Anorexia leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.5]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	NS
Anorexia leading to withdrawal 100 mg/day	8/386 [1/151]	2.1 [0.5]	2.4 (0.5 to 10.2)	0.01 (-0.01 to 0.03)	NS
Anorexia leading to withdrawal 200mg/day	**14/514 [1/202]**	**2.7 [0.5]**	**3.0 (1.0 to 9.2)**	**0.02 (0.01 to 0.04)**	**NNT 45 (25 to 192) Attributable events 22 (5 to 39)**
Anxiety leading to withdrawal 50mg/day	3/235 [0/92]	1.3 [0.0]	4.1 (0.3 to 50.6)	0.01 (-0.01 to 0.03)	NS
Anxiety leading to withdrawal 100 mg/day	**8/386 [0/151]**	**2.1 [0.2]**	**4.1 (0.9 to 19.3)**	**0.02 (0.00 to 0.04)**	**NNT 48 (26 to 284) Attributable events 21 (4 to 38)**
Anxiety leading to withdrawal 200mg/day	**9/514 [0/202]**	**1.8 [0.2]**	**4.1 (0.9 to 17.6)**	**0.02 (0.00 to 0.03)**	**NNT 57 (32 to 249) Attributable events 18 (4 to 31)**
Arthralgia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Arthralgia leading to withdrawal 100 mg/day	2/386 [0/151]	0.5 [0.0]	4.0 (0.2 to 88.2)	0.01 (-0.01 to 0.02)	NS
Arthralgia leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	NS
Back pain leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.0]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	NS
Back pain leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	NS
Depression leading to withdrawal 50mg/day	1/235 [1/92]	0.4 [0.7]	0.3 (0.0 to 7.5)	-0.01 (-0.03 to 0.02)	NS

Appendix Table 124. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults (continued)

Outcome, Daily Dose	Events/Randomized with Drug [Placebo]	Rate % with Drug [Placebo]	Peto Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm 1 Person (95% CI) Attributable Events per 1000 Treated (95% CI)
Depression leading to withdrawal 100 mg/day	3/386 [1/151]	0.8 [0.7]	1.2 (0.1 to 10.4)	0.00 (-0.01 to 0.02)	NS
Depression leading to withdrawal 200mg/day	**14/514 [1/202]**	**2.7 [0.7]**	**3.0 (0.9 to 9.2)**	**0.02 (0.01 to 0.04)**	**NNT 45 (25 to 194) Attributable events 22 (5 to 40)**
Diarrhea leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.5]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	NS
Diarrhea leading to withdrawal 100 mg/day	6/386 [1/151]	1.6 [0.5]	2.0 (0.4 to 10.5)	0.01 (-0.01 to 0.03)	NS
Diarrhea leading to withdrawal 200mg/day	10/514 [1/202]	1.9 [0.5]	2.6 (0.7 to 9.8)	0.01 (0.00 to 0.03)	NS
Dry mouth leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.5]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Dry mouth leading to withdrawal 100 mg/day	2/386 [1/151]	0.5 [0.5]	0.8 (0.1 to 9.6)	0.00 (-0.02 to 0.01)	NS
Dry mouth leading to withdrawal 200mg/day	5/514 [1/202]	1.0 [0.5]	1.8 (0.3 to 10.6)	0.00 (-0.01 to 0.02)	NS
Dyspepsia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.2]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Dyspepsia leading to withdrawal 100 mg/day	4/386 [0/151]	1.0 [0.0]	4.1 (0.5 to 36.1)	0.01 (0.00 to 0.02)	NS
Dyspepsia leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	NS
Hypesthesia leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.2]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Hypesthesia leading to withdrawal 100 mg/day	**7/386 [0/151]**	**1.8 [0.2]**	**4.1 (0.8 to 21.4)**	**0.02 (0.00 to 0.03)**	**NNT 55 (29 to 603) Attributable events 18 (2 to 35)**
Hypesthesia leading to withdrawal 200mg/day	**12/514 [0/202]**	**2.3 [0.2]**	**4.1 (1.2 to 14.6)**	**0.02 (0.01 to 0.04)**	**NNT 43 (26 to 119) Attributable events 23 (8 to 38)**
Injury leading to withdrawal 100 mg/day	1/386 [0/151]	0.3 [0.0]	4.0 (0.1 to 314.4)	0.00 (-0.01 to 0.01)	NS
Mood problems leading to withdrawal 50mg/day	2/235 [0/92]	0.9 [0.2]	4.0 (0.2 to 88.5)	0.01 (-0.01 to 0.03)	NS
Mood problems leading to withdrawal 100 mg/day	5/386 [0/151]	1.3 [0.2]	4.1 (0.6 to 28.7)	0.01 (0.00 to 0.03)	
Mood problems leading to withdrawal 200mg/day	**10/514 [0/202]**	**1.9 [0.2]**	**4.1 (1.0 to 16.4)**	**0.02 (0.01 to 0.03)**	**NNT 51 (30 to 183) Attributable events 20 (6 to 34)**

Appendix Table 124. Discontinuation due to adverse effects with topiramate in pooled analysis of individual patient data from three randomized controlled clinical trials of migraine prevention in adults (continued)

Outcome, Daily Dose	Events/Randomized with Drug [Placebo]	Rate % with Drug [Placebo]	Peto Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm 1 Person (95% CI) Attributable Events per 1000 Treated (95% CI)
Nausea leading to withdrawal 50mg/day	7/235 [1/92]	3.0 [1.1]	2.2 (0.5 to 10.5)	0.02 (-0.01 to 0.05)	NS
Nausea leading to withdrawal 100 mg/day	9/386 [2/151]	2.3 [1.1]	1.7 (0.4 to 6.2)	0.01 (-0.01 to 0.03)	NS
Nausea leading to withdrawal 200mg/day	**29/514 [2/202]**	**5.6 [1.1]**	**3.1 (1.4 to 6.8)**	**0.05 (0.02 to 0.07)**	**NNT 22 (14 to 45) Attributable events 47 (23 to 71)**
Pharyngitis leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Pharyngitis leading to withdrawal 100 mg/day	2/386 [0/151]	0.5 [0.0]	4.0 (0.2 to 88.2)	0.01 (-0.01 to 0.02)	NS
Sinusitis leading to withdrawal 200mg/day	1/514 [0/202]	0.2 [0.0]	4.0 (0.1 to 313.6)	0.00 (-0.01 to 0.01)	NS
Weight loss leading to withdrawal 50mg/day	1/235 [0/92]	0.4 [0.0]	4.0 (0.1 to 314.3)	0.00 (-0.01 to 0.02)	NS
Weight loss leading to withdrawal 100 mg/day	4/386 [0/151]	1.0 [0.0]	4.1 (0.5 to 36.1)	0.01 (0.00 to 0.02)	NS
Weight loss leading to withdrawal 200mg/day	6/514 [0/202]	1.2 [0.0]	4.1 (0.7 to 24.2)	0.01 (0.00 to 0.02)	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Approved drugs				
Topiramate 200mg Adelman, 2008	Hypesthesia	715 Risk of bias Low	9.8 (0.6 to 164.8)	**0.02 (0.01 to 0.04)**
Topiramate 200mg Adelman, 2008[40]	Dry mouth	716 Risk of bias Low	2.0 (0.2 to 16.7)	0.00 (-0.01 to 0.02)
Topiramate 200mg Adelman, 2008[40]	Mood problems	715 Risk of bias Low	8.2 (0.5 to 139.9)	**0.02 (0.01 to 0.03)**
Topiramate 200mg Adelman, 2008[40]	Weight decrease	716 Risk of bias Low	5.1 (0.3 to 90.5)	0.01 (0.00 to 0.02)
Topiramate 200mg Adelman, 2008[40]	Abdominal pain	716 Risk of bias Low	2.4 (0.5 to 10.4)	0.01 (-0.01 to 0.03)
Topiramate 200mg Adelman, 2008[40]	Anorexia	716 Risk of bias Low	5.5 (0.7 to 41.6)	**0.02 (0.01 to 0.04)**
Topiramate 200mg Adelman, 2008[40]	Diarrhea	716 Risk of bias Low	3.9 (0.5 to 30.5)	0.01 (0.00 to 0.03)
Topiramate 200mg Adelman, 2008[40]	Dyspepsia	716 Risk of bias Low	1.2 (0.0 to 28.9)	0.00 (-0.01 to 0.01)
Topiramate 100mg Lainez, 2007[35]	Nausea	774 Risk of bias Low	1.8 (0.6 to 5.2)	0.01 (-0.01 to 0.03)
Topiramate 100mg Adelman, 2008[40]	Pharyngitis	537 Risk of bias Low	2.0 (0.1 to 40.7)	0.01 (-0.01 to 0.02)
Topiramate 200mg Adelman, 2008[40]	Sinusitis	716 Risk of bias Low	1.2 (0.0 to 28.9)	0.00 (-0.01 to 0.01)
Topiramate 200mg Freitag, 2007[36]	Upper respiratory tract infection	304 Risk of bias Low	0.0 (0.0 to 0.0)	0.00 (-0.02 to 0.02)
Topiramate 100mg Adelman, 2008[40]	Injury	537 Risk of bias Low	1.2 (0.0 to 28.8)	0.00 (-0.01 to 0.01)
Topiramate 200mg Adelman, 2008[40]	Arthralgia	716 Risk of bias Low	1.2 (0.0 to 28.9)	0.00 (-0.01 to 0.01)
Topiramate 200mg Adelman, 2008[40]	Back pain	716 Risk of bias Low	1.2 (0.0 to 28.9)	0.00 (-0.01 to 0.01)
Topiramate 200mg Adelman, 2008[40]	Abnormal vision	716 Risk of bias Low	4.3 (0.2 to 78.1)	0.01 (0.00 to 0.02)
Topiramate 75mg Bavrasad, 2010[232]	Paresthesia	70 Risk of bias Medium	3.0 (0.1 to 71.2)	0.03 (-0.05 to 0.10)
Topiramate 75mg Bavrasad, 2010[232]	Nausea	70 Risk of bias Medium	0.3 (0.0 to 7.9)	-0.03 (-0.10 to 0.05)
Topiramate 200mg Diener, 2004[43]	Fatigue	288 Risk of bias Low	1.7 (0.8 to 3.7)	0.04 (-0.02 to 0.11)

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials (continued)

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Topiramate 200mg Diener, 2004[43]	Difficulty with memory	288 Risk of bias Low	3.0 (0.3 to 28.5)	0.01 (-0.01 to 0.04)
Topiramate 200mg Diener, 2004[43]	Insomnia	288 Risk of bias Low	2.0 (0.7 to 5.7)	0.03 (-0.02 to 0.09)
Topiramate 200mg Diener, 2004[43]	Somnolence	288 Risk of bias Low	0.7 (0.1 to 3.9)	-0.01 (-0.04 to 0.02)
Topiramate 100mg Diener, 2004[43]	Taste perversion	285 Risk of bias Low	0.0 (0.0 to 0.0)	0.00 (-0.01 to 0.01)
Topiramate 200mg Diener, 2004[43]	Weight decrease	288 Risk of bias Low	7.0 (0.4 to 134.3)	0.02 (-0.01 to 0.05)
Topiramate 200mg Diener, 2004[43]	Nausea	288 Risk of bias Low	3.2 (1.2 to 8.5)	0.08 (0.02 to 0.14)
Divalproex sodium 1000 mg Klapper, 1997[47]	Abdominal pain	87 Risk of bias Low	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.09)
Divalproex sodium 1500 mg Klapper, 1997[47]	Alopecia	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Back pain	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 500 mg Klapper, 1997[47]	Constipation	89 Risk of bias Low	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Emotional liability	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Gastrointestinal disorder	58 Risk of bias Low	0.0 (0.0 to 0.0)	0.00 (-0.10 to 0.10)
Divalproex sodium 1500 mg Klapper, 1997[47]	Nausea	88 Risk of bias Low	9.0 (0.5 to 162.3)	0.09 (0.00 to 0.18)
Divalproex sodium 1000 mg Klapper, 1997[47]	Pharyngitis	87 Risk of bias Low	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.09)
Divalproex sodium 500 mg Klapper, 1997[47]	Pneumonia	89 Risk of bias Low	2.9 (0.1 to 70.2)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Somnolence	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Thinking abnormal	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Vomiting	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Weight increase (gain)	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)
Divalproex sodium 1500 mg Klapper, 1997[47]	Diarrhea	88 Risk of bias Low	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.08)

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials (continued)

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Dry mouth	86 Risk of bias Medium	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Tremor	86 Risk of bias Medium	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Vertigo	86 Risk of bias Medium	5.0 (0.2 to 101.2)	0.05 (-0.03 to 0.12)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Weight increase (gain)	86 Risk of bias Medium	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Abdominal pain	86 Risk of bias Medium	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Appetite increase	86 Risk of bias Medium	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Sodium valproate 1000mg to 1500 mg per day Jensen, 1994[49]	Nausea	86 Risk of bias Medium	7.0 (0.4 to 131.6)	0.07 (-0.02 to 0.16)
Timolol 10mg twice a day Stellar, 1984[79]	Any adverse event	94 Risk of bias Medium	5.0 (0.2 to 101.4)	0.04 (-0.03 to 0.11)
Timolol 10mg twice a day Stellar, 1984[79]	Chest pain(moderate) on day 28	94 Risk of bias Medium	3.0 (0.1 to 71.8)	0.02 (-0.04 to 0.08)
Timolol 10mg twice a day Stellar, 1984[79]	Epigastric distress(severe) and fecal impaction	94 Risk of bias Medium	3.0 (0.1 to 71.8)	0.02 (-0.04 to 0.08)
Propranolol 160 mg/d Diener, 2004[43]	**Fatigue**	**290 Risk of bias Low**	**19.3 (1.1 to 327.9)**	**0.06 (0.02 to 0.10)**
Propranolol 160 mg/d Diener, 2004[43]	Difficulty with memory	290 Risk of bias Low	3.0 (0.1 to 74.0)	0.01 (-0.01 to 0.03)
Propranolol 160 mg/d Diener, 2004[43]	Somnolence	193 Risk of bias Low	2.4 (0.1 to 45.9)	0.02 (-0.02 to 0.06)
Propranolol 160 mg/d Diener, 2004[43]	Weight decrease	290 Risk of bias Low	0.0 (0.0 to 0.0)	0.00 (-0.01 to 0.01)
Propranolol 160 mg/d Diener, 2004[43]	Nausea	193 Risk of bias Low	1.7 (0.2 to 14.2)	0.01 (-0.04 to 0.06)
Propranolol 160 mg Pradalier, 1989[53]	Psoriasis	55 Risk of bias Low	0.3 (0.0 to 6.1)	-0.04 (-0.14 to 0.06)

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials (continued)

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Off label drugs				
Acetazolamide 500 mg Vahedi, 2002[80]	Discontinued due to adverse event	53 Risk of bias Low	4.7 (1.1 to 19.6)	0.27 (0.06 to 0.48)
Carbamazepine Rompel, 1970[86]	Discontinued due to adverse event	96 Risk of bias Medium	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)
Lamotrigine 25 mg-200 mg Steiner, 1997[87]	Dizziness	58 Risk of bias Low	6.5 (0.3 to 151.7)	0.06 (-0.07 to 0.18)
Lamotrigine 26 mg-200 mg Steiner, 1997[87]	Dyspepsia	59 Risk of bias Low	0.7 (0.0 to 16.0)	-0.03 (-0.11 to 0.06)
Lamotrigine 27 mg-200 mg Steiner, 1997[87]	Nausea	58 Risk of bias Low	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)
Lamotrigine 28 mg-200 mg Steiner, 1997[87]	Leucopenia	58 Risk of bias Low	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)
Lamotrigine 29 mg-200 mg Steiner, 1997[87]	**Rash**	**58 Risk of bias Low**	**15.6 (2.1 to 117.3)**	**0.36 (0.13 to 0.59)**
Oxcarbazepine up to 1,200 mg Silberstein, 2008[83]	Discontinued due to adverse event	170 Risk of bias Low	2.0 (0.6 to 6.4)	0.05 (-0.03 to 0.12)
Femoxetine 200 mg-400mg Kangasniemi, 1983[77]	Discontinued due to adverse event	58 Risk of bias Medium	7.0 (0.4 to 129.7)	0.10 (-0.02 to 0.23)
Tonabersat 20 mg-40 mg Goadsby, 2009[121]	Discontinued due to adverse event	124 Risk of bias Low	2.2 (0.2 to 23.7)	0.02 (-0.04 to 0.07)
Tonabersat 20 mg-40 mg Goadsby, 2009[121]	Dizziness	124 Risk of bias Low	1.8 (0.5 to 7.4)	0.04 (-0.05 to 0.13)
Atenolol 100mg Johannsson, 1987[99]	Discontinued due to adverse event	144 Risk of bias Medium	0.1 (0.0 to 2.7)	-0.04 (-0.09 to 0.01)
Bisoprolol 100mg van de Ven, 1997[101]	Discontinued due to adverse event	115 Risk of bias Medium	1.7 (0.4 to 7.9)	0.04 (-0.06 to 0.13)
Metoprolol 200mg Andersson, 1983[97]	Discontinued due to adverse event	71 Risk of bias Medium	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.08)
Nadolol 80mg -240mg Freitag, 1984[98]	Bradycardia	32 Risk of bias Low	1.1 (0.0 to 24.2)	0.04 (-0.13 to 0.22)
Pindolol 7.5 -15mg Sjaastad, 1972[89]	Discontinued due to adverse event	56 Risk of bias Medium	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.23)
Nicardipine 40mg Leandri, 1990[126]	Dyspepsia	60 Risk of bias Medium	0.5 (0.0 to 5.2)	-0.03 (-0.14 to 0.08)
Verapamil 240mg Markley, 1984[124]	Constipation	40 Risk of bias Medium	3.0 (0.1 to 69.5)	0.05 (-0.08 to 0.18)
Dihydroergotamine 10mg Bousser, 1988[233]	Intolerance(alleged)	90 Risk of bias Medium	0.1 (0.0 to 2.7)	-0.07 (-0.15 to 0.02)

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials (continued)

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Lisuride 0.075 mg Somerville, 1976[158]	Discontinued due to adverse event	150 Risk of bias Medium	2.4 (0.9 to 6.5)	0.09 (-0.01 to 0.19)
Lisuride 0.075 mg Somerville, 1976[158]	Fatigue, weakness	150 Risk of bias Medium	7.0 (0.4 to 133.2)	0.04 (-0.01 to 0.09)
Lisuride 0.075 mg Somerville, 1976[158]	Hallucinations	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Numbness of tongue	150 Risk of bias Medium	0.3 (0.0 to 8.1)	-0.01 (-0.05 to 0.02)
Lisuride 0.075 mg Somerville, 1976[158]	Somnolence (Drowsiness)	150 Risk of bias Medium	1.0 (0.1 to 15.7)	0.00 (-0.04 to 0.04)
Lisuride 0.075 mg Somerville, 1976[158]	Vertigo	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Chest pains	150 Risk of bias Medium	2.0 (0.2 to 21.6)	0.01 (-0.03 to 0.06)
Lisuride 0.075 mg Somerville, 1976[158]	Subcutaneous hemorrhage	150 Risk of bias Medium	0.5 (0.0 to 5.4)	-0.01 (-0.06 to 0.03)
Lisuride 0.075 mg Somerville, 1976[158]	Blurred vision	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Eye irritation	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Nausea	150 Risk of bias Medium	1.0 (0.1 to 6.9)	0.00 (-0.05 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Back pains	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Lisuride 0.075 mg Somerville, 1976[158]	Impotence	150 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Methysergide 1 mg q.d.s. Whewell, 1966[154]	Discontinued due to adverse event	148 Risk of bias Medium	0.5 (0.0 to 5.4)	-0.01 (-0.06 to 0.03)
Methysergide 1 mg q.d.s. Whewell, 1966[154]	Nausea(excessive)	148 Risk of bias Medium	3.0 (0.1 to 72.5)	0.01 (-0.02 to 0.05)
Tizanidine 4mg Saper, 2002[234]	Adverse event other than death	136 Risk of bias Medium	2.0 (0.6 to 6.2)	0.06 (-0.03 to 0.16)
Tizanidine 4mg Saper, 2002[234]	Headache	136 Risk of bias Medium	2.7 (0.1 to 64.4)	0.01 (-0.02 to 0.05)
Fenoprofen 600 mg TID CN-00048653	Fatigue	75 Risk of bias Medium	0.9 (0.1 to 14.2)	0.00 (-0.08 to 0.07)
Fenoprofen 600 mg TID Solomon, 1987[198]	Adverse effects: fatigue and/or somnolence	Risk of bias Low	0.9 (0.1 to 14.2)	0.00 (-0.08 to 0.07)
Fenoprofen 600 mg TID Diamond, 1987[235]	Gastrointestinal symptoms	75 Risk of bias Medium	2.8 (0.3 to 25.4)	0.05 (-0.05 to 0.15)

Appendix Table D125. Treatment discontinuation due to adverse effects with approved and off label drugs vs. placebo, results from individual randomized controlled clinical trials (continued)

Active Drug, Daily Dose Reference	Adverse Effect that Resulted in Treatment Discontinuation	Sample Size Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Tolfenamic Acid 300mg Mikkelsen, 1982[202]	Discontinued due to adverse event	76 Risk of bias Medium	2.0 (0.2 to 21.1)	0.03 (-0.06 to 0.11)
Montelukast 20 mg Brandes, 2004[203]	Discontinued due to adverse event	177 Risk of bias Low	0.9 (0.1 to 6.3)	0.00 (-0.05 to 0.04)

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D126. Adverse effects with topiramate in adults with migraine (pooled with random effects models—results from randomized controlled clinical trials)

Outcome, Reference	Sample	Rate with Topiramate [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Adverse events[29, 31, 34, 40, 42, 44]	**1700**	**59.9 [56.1]**	**2.0 (1.1 to 3.5)**	**0.12 (0.02 to 0.22)**	**8 (4 to 42)**	**124 (24 to 223)**
Paresthesia[18, 20, 24, 28, 29, 31, 34, 40, 42, 44]	**1876**	**24.0 [5.5]**	**6.8 (4.8 to 9.7)**	**0.24 (0.14 to 0.33)**	**4 (3 to 7)**	**235 (142 to 328)**
Weight decrease[18, 24, 28, 29, 38, 40]	**1648**	**12.3 [4.4]**	**4.7 (1.7 to 12.6)**	**0.10 (0.05 to 0.15)**	**10 (6 to 19)**	**104 (53 to 154)**
Cognitive difficulties[24, 28, 31, 34, 38, 40, 43]	**1782**	**8 [3]**	**2.3 (1.1 to 4.8)**	**0.045 (0.01 to 0.08)**	**22 (13 to 100)**	**45 (10 to 80)**
Diarrhea[19, 40, 42]	**1170**	**9.8 [3.6]**	**2.9 (1.6 to 5.2)**	**0.06 (0.01 to 0.10)**	**18 (10 to 71)**	**57 (14 to 100)**
Dry mouth[40-42]	**1429**	**6.1 [2.7]**	**2.6 (1.4 to 4.6)**	**0.04 (0.01 to 0.06)**	**29 (18 to 71)**	**35 (14 to 57)**
Fatigue[34, 40]	**1857**	**9.6 [4.6]**	**1.8 (1.3 to 2.6)**	**0.05 (0.03 to 0.08)**	**20 (13 to 38)**	**50 (26 to 75)**
Hyperesthesia[31, 40, 42]	**1756**	**7.4 [1.6]**	**3.7 (1.9 to 7.1)**	**0.06 (0.03 to 0.08)**	**18 (13 to 30)**	**57 (33 to 80)**
Insomnia[19, 25, 28, 43]	**878**	**4 [2]**	**1.7 (0.5 to 5.1)**	**0.021 (0.001 to 0.042)**		**21 (1 to 42)**
Memory impairment[19, 28, 29, 34, 40, 41, 43]	**1436**	**10.4 [3.9]**	**2.5 (1.2 to 5.3)**	**0.058 (0.017 to 0.099)**	**17 (10 to 59)**	**58 (17 to 99)**
Nausea[29, 31, 38, 40, 42, 43]	**2156**	**11 [6]**	**1.6 (1.1 to 2.2)**	**0.034 (0.003 to 0.065)**	**29 (15 to 333)**	**34 (3 to 65)**
Taste perversion[18, 24, 28, 40-43]	**1634**	**5.9 [1.3]**	**5.5 (2.7 to 11.1)**	**0.083 (0.025 to 0.14)**	**12 (7 to 40)**	**83 (25 to 140)**
Abdominal pain [38, 40]	1229	2.0 [2.3]	0.9 (0.4 to 2.0)	0.00 (-0.02 to 0.02)		
Anorexia[18, 28, 29, 31, 34, 38, 40, 42, 44]	2424	5.6 [3.3]	1.8 (1.2 to 2.9)	0.03 (0.00 to 0.05)		
Back pain[40, 42]	1100	4.6 [5.1]	0.9 (0.5 to 1.7)	0.00 (-0.03 to 0.02)		
Giddiness[28, 29, 31, 34, 40, 42, 44]	1871	10.1 [7.8]	1.2 (0.7 to 1.8)	0.01 (-0.02 to 0.04)		
Dyspepsia[34, 40]	1018	1.5 [1.1]	1.3 (0.4 to 3.8)	0.01 (-0.03 to 0.05)		
Infection, viral[34, 42]	444	8.2 [8.0]	1.0 (0.5 to 2.1)	0.00 (-0.05 to 0.05)		
Injury[31, 40, 42]	1672	5.0 [6.1]	0.8 (0.2 to 3.4)	-0.01 (-0.07 to 0.04)		
Adverse events: Serious[38, 41]	842	7.9 [6.6]	1.1 (0.5 to 2.3)	0.01 (-0.05 to 0.06)		
Sinusitis[31, 40, 42]	1429	7.4 [6.4]	1.1 (0.7 to 1.8)	0.01 (-0.02 to 0.03)		
Sleepiness[20, 24, 28, 29, 34, 40-42]	1893	4.4 [3.4]	1.6 (0.8 to 3.2)	0.02 (-0.01 to 0.04)		
Language problems: Treatment - emergent adverse events[19, 28, 40]	657	3.6 [0.5]	5.1 (1.2 to 22.8)	0.09 (-0.03 to 0.21)		
Upper respiratory tract infection[29, 40-42]	1641	8.7 [9.0]	1.0 (0.7 to 1.5)	0.00 (-0.03 to 0.03)		
Vision, abnormal[18, 40]	756	7.7 [2.2]	3.5 (1.4 to 8.5)	0.07 (-0.01 to 0.15)		

Bold = significant at 95% confidence limit when 95% CI of relative measure of the association estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

CI = confidence interval

Appendix Table D127. Significant increase in risk of adverse effects with migraine preventive drugs vs. placebo, results from individual RCTs

Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active Drugs [Placebo]	Relative Risk (95%CI)	Absolute Risk Difference (95%CI)	Number Needed to Treat (95%C)	Attributable Events (95%CI)
Topiramate	Mood problems	Low Adelman, 2008[40]	716	5.4 [1.8]	2.8 (1.0 to 7.7)	0.03 (0.01 to 0.06)	29 (16 to 139)	35 (7 to 62)
Topiramate	Paresthesia: Moderate	Low Adelman, 2008[40]	716	12.6 [1.4]	8.5 (2.7 to 26.8)	0.11 (0.08 to 0.14)	9 (7 to 13)	112 (78 to 145)
Topiramate	Nausea: Mild/moderate	Low Bussone, 2005[25]	758	11.1 [6.5]	1.7 (1.1 to 2.8)	0.05 (0.01 to 0.09)	21 (11 to 148)	47 (7 to 87)
Topiramate	Anorexia: Severe	Low Bussone, 2005[25]	758	1.3 [0.0]	10.6(0.6 to 191.1)	0.01 (0.00 to 0.03)	77 (39 to 1695)	13 (1 to 25)
Topiramate	Low bicarbonate values that met the study-defined criteria for markedly abnormal laboratory values	Low Lipton, 2011[42]	385	7.4 [0.0]	30.4 (1.8 to 505.7)	0.07 (0.04 to 0.11)	13 (9 to 28)	74 (36 to 113)
Divalproex	Hair loss(Alopecia)	Medium Mathew, 1995[45]	107	12.9 [0.0]	10.2 (0.6 to 170.0)	0.13 (0.04 to 0.22)	8 (5 to 24)	129 (41 to 216)
Propranolol	Weight increase >2kg	Medium Forssman, 1976[52]	80	12.5 [0.0]	11.0 (0.6 to 192.6)	0.1 (0.02 to 0.23)	8 (4 to 65)	125 (15 to 235)
Propranolol	Bradycardia	Medium Nadelmann, 1986[236]	114	8.8 [0.0]	11.0 (0.6 to 194.4)	0.09 (0.01 to 0.17)	11 (6 to 116)	88 (9 to 167)
Propranolol	Epigastric distress	Medium Nadelmann, 1986[236]	114	19.3 [3.5]	5.5 (1.3 to 23.7)	0.16 (0.04 to 0.27)	6 (4 to 22)	158 (45 to 271)
Propranolol	Malaise	Medium Nadelmann, 1986[236]	114	15.8 [3.5]	4.5 (1.0 to 19.9)	0.12 (0.02 to 0.23)	8 (4 to 60)	123 (17 to 229)
Acetazolamide	Fatigue, drowsiness, memory impairment	Low Vahedi, 2002[80]	53	57.7 [14.8]	3.9 (1.5 to 10.2)	0.43 (0.20 to 0.66)	2 (2 to 5)	429 (196 to 661)
Acetazolamide	Paresthesia	Low Vahedi, 2002[80]	53	80.8 [7.4]	10.9 (2.8 to 41.9)	0.73 (0.55 to 0.91)	1 (1 to 2)	734 (553 to 914)
Carbamazepine	Total adverse effects	Medium Rompel, 1970[86]	96	62.5 [22.9]	2.7 (1.6 to 4.8)	0.40 (0.21 to 0.58)	3 (2 to 5)	396 (214 to 577)
Carbamazepine	Sleepiness	Medium Rompel, 1970[86]	96	10.4 [0.0]	11.0 (0.6 to 193.6)	0.10 (0.01 to 0.20)	10 (5 to 88)	104 (11 to 197)
Carbamazepine	Vertigo or giddiness	Medium Rompel, 1970[86]	96	47.9 [4.2]	11.5 (2.9 to 46.1)	0.44 (0.29 to 0.59)	2 (2 to 4)	438 (285 to 590)
Oxcarbazepine	Total adverse effects	Unclear Silberstein, 2008[83]	170	80.0 [64.7]	1.2 (1.0 to 1.5)	0.15 (0.02 to 0.29)	7 (4 to 49)	153 (20 to 285)

Appendix Table D127. Significant increase in risk of adverse effects with migraine preventive drugs vs. placebo, results from individual RCTs (continued)

Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active Drugs [Placebo]	Relative Risk (95%CI)	Absolute Risk Difference (95%CI)	Number Needed to Treat (95%C)	Attributable Events (95%CI)
Oxcarbazepine	Dizziness	Unclear Silberstein, 2008[83]	170	17.6 [7.1]	2.5 (1.0 to 6.1)	0.11 (0.01 to 0.20)	9 (5 to 121)	106 (8 to 204)
Oxcarbazepine	Fatigue	Unclear Silberstein, 2008[83]	170	20.0 [7.1]	2.8 (1.2 to 6.8)	0.13 (0.03 to 0.23)	8 (4 to 35)	129 (28 to 230)
Oxcarbazepine	Nausea	Unclear Silberstein, 2008[83]	170	16.5 [4.7]	3.5 (1.2 to 10.2)	0.12 (0.03 to 0.21)	8 (5 to 37)	118 (27 to 208)
Atenolol	Dizziness(slight) of orthostatic type during first week	Medium Forssman, 1982[95]	48	25.0 [4.2]	6.0 (0.8 to 46.1)	0.21 (0.02 to 0.40)	5 (3 to 57)	208 (18 to 399)
Pindolol	Dizziness/faintness (orthostatic)	Medium Sjaastad, 1972[89]	56	21.4 [0.0]	13.0 (0.8 to 220.3)	0.21 (0.06 to 0.37)	5 (3 to 18)	214 (55 to 373)
Metoprolol	Adverse events	Medium Kangasniemi, 1987[100]	154	55.8 [27.3]	2.0 (1.4 to 3.1)	0.29 (0.14 to 0.43)	3 (2 to 7)	286 (137 to 435)
Metoprolol	Fatigue/tiredness	Medium Kangasniemi, 1987[100]	154	16.9 [5.2]	3.3 (1.1 to 9.5)	0.12 (0.02 to 0.21)	9 (5 to 51)	117 (20 to 214)
Metoprolol	Gastrointestinal adverse events	Medium Kangasniemi, 1987[100]	154	20.8 [3.9]	5.3 (1.6 to 17.6)	0.17 (0.07 to 0.27)	6 (4 to 15)	169 (68 to 269)
Lisinopril	Total adverse effects	Low Schrader, 2001[136]	120	40.0 [21.7]	1.8 (1.0 to 3.3)	0.18 (0.02 to 0.35)	5 (3 to 47)	183 (21 to 345)
Clonidine	Total adverse effects	Medium Shafar, 1972[142]	130	55.4 [26.2]	2.1 (1.3 to 3.4)	0.29 (0.13 to 0.45)	3 (2 to 8)	292 (131 to 454)
Amitriptyline	Adverse events: Severe	Medium Couch, 2011[111]	391	15.5 [5.1]	3.0 (1.5 to 6.1)	0.10 (0.04 to 0.16)	10 (6 to 22)	104 (44 to 163)
Amitriptyline	Body as a whole	Medium Couch, 2011[111]	391	12.9 [6.6]	2.0 (1.0 to 3.7)	0.06 (0.00 to 0.12)	16 (8 to 230)	63 (4 to 121)
Amitriptyline	Integument	Medium Couch, 2011[111]	391	35.1 [9.1]	3.8 (2.4 to 6.2)	0.26 (0.18 to 0.34)	4 (3 to 6)	259 (181 to 337)
Amitriptyline	Psychiatric	Medium Couch, 2011[111]	391	31.4 [15.2]	2.1 (1.4 to 3.0)	0.16 (0.08 to 0.24)	6 (4 to 13)	162 (80 to 245)
Amitriptyline	Digestive	Medium Couch, 2011[111]	391	14.4 [7.6]	1.9 (1.0 to 3.4)	0.07 (0.01 to 0.13)	15 (8 to 156)	68 (6 to 130)
Amitriptyline	Urogenital Urinary retention	Medium Couch, 2011[111]	391	3.1 [0.0]	13.2 (0.7 to 232.7)	0.03 (0.00 to 0.06)	32 (18 to 209)	31 (5 to 57)
Fluoxetine	Tremor	Medium Saper, 1994[117]	111	19.7 [6.0]	3.3 (1.0 to 11.0)	0.14 (0.02 to 0.26)	7 (4 to 58)	137 (17 to 256)
Fluoxetine	Stomach pain	Medium Saper, 1994[117]	111	13.1 [0.0]	14.0 (0.8 to 236.5)	0.13 (0.04 to 0.22)	8 (5 to 24)	131 (41 to 221)

Appendix Table D127. Significant increase in risk of adverse effects with migraine preventive drugs vs. placebo, results from individual RCTs (continued)

Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active Drugs [Placebo]	Relative Risk (95%CI)	Absolute Risk Difference (95%CI)	Number Needed to Treat (95%C)	Attributable Events (95%CI)
Fluoxetine	Pyrosis	Medium d'Amato, 1999[119]	52	21.9 [0.0]	9.5 (0.6 to 158.5)	0.22 (0.06 to 0.38)	5 (3 to 16)	219 (62 to 376)
Venlafaxine	Vomiting	Medium Ozyalcin, 2005[122]	40	23.8 [0.0]	10.0 (0.6 to 169.6)	0.24 (0.04 to 0.43)	4 (2 to 22)	238 (45 to 432)
Dihydro-ergotamine	Nausea, sleepiness, mild gastralgias and abdominal discomfort	Medium Bousser, 1988[233]	90	13.3 [2.2]	6.0 (0.8 to 47.8)	0.11 (0.00 to 0.22)	9 (5 to 350)	111 (3 to 219)
Magnesium	Total adverse effects	Low Pfaffenrath, 1996	69	45.7 [23.5]	1.9 (1.0 to 3.9)	0.22 (0.00 to 0.44)	5 (2 to 267)	222 (4 to 440)
Tizanidine	Dizziness	Medium Saper, 2002[234]	136	23.6 [6.3]	3.8 (1.3 to 10.6)	0.17 (0.06 to 0.29)	6 (3 to 17)	174 (59 to 288)
Tizanidine	Dry mouth	Medium Saper, 2002[234]	136	22.2 [1.6]	14.2 (1.9 to 104.3)	0.21 (0.11 to 0.31)	5 (3 to 9)	207 (106 to 307)
Tizanidine	Asthenia	Medium Saper, 2002[234]	136	19.4 [3.1]	6.2 (1.5 to 26.3)	0.16 (0.06 to 0.26)	6 (4 to 16)	163 (62 to 264)
Tizanidine	Sleepiness	Medium Saper, 2002[234]	136	45.8 [4.7]	9.8 (3.1 to 30.4)	0.41 (0.29 to 0.54)	2 2 to 4)	411 (285 to 538)
Indomethacin	Insomnia	Medium Anthony, 1968[200]	38	26.3 [0.0]	11.0 (0.7 to 186.0)	0.26 (0.06 to 0.47)	4 (2 to 18)	263 (56 to 470)
Indomethacin	Indigestion	Medium Anthony, 1968[200]	38	36.8 [5.3]	7.0 (1.0 to 51.5)	0.32 (0.08 to 0.55)	3 (2 to 13)	316 (77 to 555)
Nifedipine	Total adverse effects	High McArthur, 1989[129]	48	54.2 [8.3]	6.5 (1.6 to 25.8)	0.46 (0.23 to 0.69)	2 (1 to 4)	458 (230 to 686)
Nifedipine	Dizziness	High McArthur, 1989[129]	48	45.8 [0.0]	23.0 (1.4 to 369.5)	0.46 (0.26 to 0.66)	2 (2 to 4)	458 (255 to 661)
Nifedipine	Headache	High McArthur, 1989[129]	48	16.7 [0.0]	9.0 (0.5 to 158.5)	0.17 (0.01 to 0.33)	6 (3 to 157)	167 (6 to 327)
Nimodipine	Abdominal cramps	Medium Gelmers, 1983[127]	60	16.7 [0.0]	11.0 (0.6 to 190.5)	0.17 (0.03 to 0.31)	6 (3 to 40)	167 (25 to 308)
Verapamil	Constipation	Medium Markley, 1984[124]	40	30.0 [0.0]	13.0 (0.8 to 216.4)	0.30 (0.09 to 0.51)	3 (2 to 11)	300 (92 to 508)
Nifedipine	Edema	High McArthur, 1989[129]	48	45.8 [0.0]	23.0 (1.4 to 369.5)	0.46 (0.26 to 0.66)	2 (2 to 4)	458 (255 to 661)
Tonabersat	Total adverse effects	Low 19222510	124	39.0 [15.4]	2.5 (1.3 to 4.9)	0.24 (0.08 to 0.39)	4 (3 to 12)	236 (84 to 388)
Tonabersat	Vertigo	Low Goadsby, 2009[121]	124	8.5 [0.0]	12.1 (0.7 to 214.2)	0.08 (0.01 to 0.16)	12 (6 to 114)	85 (9 to 161)

Appendix Table D128. Dose response adverse effects with topiramate in adults

Adverse effect	Reference Risk of Bias	Active vs. Control Daily Dose	Events/Randomized (Rate of Outcome in Active Group) Events/Randomized (Rate of Outcome in Control Group)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Abnormal vision	Adelman, 2008[40] Risk of bias Low	200 vs. 50	6/514 (1.2) 12/235 (5.1)	0.2 (0.1 to 0.6)	-0.04 (-0.07 to -0.01)
Abnormal vision	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**38/514 (7.4) 14/386 (3.6)**	**2.0 (1.1 to 3.7)**	**0.04 (0.01 to 0.07)**
Anorexia	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**56/386 (14.5) 22/235 (9.4)**	**1.5 (1.0 to 2.5)**	**0.05 (0.00 to 0.10)**
Anorexia leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**14/514 (2.7) 2/235 (0.9)**	**3.2 (0.7 to 14.0)**	**0.02 (0.00 to 0.04)**
Any adverse event	Adelman, 2008[40] Risk of bias Low	200 vs. 100	187/514 (36.4) 227/386 (58.8)	0.6 (0.5 to 0.7)	-0.22 (-0.29 to -0.16)
Arthralgia	Adelman, 2008[40] Risk of bias Low	100 vs. 50	11/386 (2.8) 17/235 (7.2)	0.4 (0.2 to 0.8)	-0.04 (-0.08 to -0.01)
Arthralgia	Adelman, 2008[40] Risk of bias Low	200 vs. 50	7/514 (1.4) 17/235 (7.2)	0.2 (0.1 to 0.4)	-0.06 (-0.09 to -0.02)
Arthralgia	Adelman, 2008[40] Risk of bias Low	200 vs. 50	4/514 (0.8) 8/235 (3.4)	0.2 (0.1 to 0.8)	-0.03 (-0.05 to 0.00)
Depression leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**14/514 (2.7) 1/235 (0.4)**	**6.4 (0.8 to 48.4)**	**0.02 (0.01 to 0.04)**
Depression leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**14/514 (2.7) 3/386 (0.8)**	**3.5 (1.0 to 12.1)**	**0.02 (0.00 to 0.04)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**8/386 (2.1) 1/235 (0.4)**	**4.9 (0.6 to 38.7)**	**0.02 (0.00 to 0.03)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**24/514 (4.7) 1/235 (0.4)**	**11.0 (1.5 to 80.6)**	**0.04 (0.02 to 0.06)**
Difficulty in memory leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**24/514 (4.7) 8/386 (2.1)**	**2.3 (1.0 to 5.0)**	**0.03 (0.00 to 0.05)**
Difficulty with concentration/attention	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**51/514 (9.9) 7/235 (3.0)**	**3.3 (1.5 to 7.2)**	**0.07 (0.04 to 0.10)**
Difficulty with concentration/attention	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**51/514 (9.9) 23/386 (6.0)**	**1.7 (1.0 to 2.7)**	**0.04 (0.00 to 0.07)**
Difficulty with memory	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**57/514 (11.1) 26/386 (6.7)**	**1.6 (1.1 to 2.6)**	**0.04 (0.01 to 0.08)**
Dry mouth	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**26/514 (5.1) 4/235 (1.7)**	**3.0 (1.0 to 8.4)**	**0.03 (0.01 to 0.06)**
Hypoesthesia leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**12/514 (2.3) 1/235 (0.4)**	**5.5 (0.7 to 41.9)**	**0.02 (0.00 to 0.03)**

Appendix Table 128. Significant dose response adverse effects with topiramate in adults (continued)

Adverse effect	Reference Risk of Bias	Active vs. Control Daily Dose	Events/Randomized (Rate of Outcome in Active Group) Events/Randomized (Rate of Outcome in Control Group)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Marked anorexia	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**6/514 (1.2) 0/235 (0.0)**	**6.0 (0.3 to 105.3)**	**0.01 (0.00 to 0.02)**
Marked fatigue	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**6/386 (1.6) 0/235 (0.0)**	**7.9 (0.4 to 140.1)**	**0.02 (0.00 to 0.03)**
Marked fatigue	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**15/514 (2.9) 0/235 (0.0)**	**14.2 (0.9 to 236.4)**	**0.03 (0.01 to 0.05)**
Marked paresthesia	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**20/514 (3.9) 3/235 (1.3)**	**3.0 (0.9 to 10.2)**	**0.03 (0.00 to 0.05)**
Markedly low serum bicarbonate levels (range >5mmol/L to <17mmo/L below baseline)	Adelman, 2008[40] Risk of bias Low	50 vs. 0	5/235 (2.0) 57/514 (11.0)	0.2 (0.1 to 0.5)	-0.09 (-0.12 to -0.06)
Markedly low serum bicarbonate levels (range >5mmol/L to <17mmo/L below baseline)	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**35/386 (9.0) 5/235 (2.0)**	**4.3 (1.7 to 10.7)**	**0.07 (0.04 to 0.10)**
Mild paresthesia	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**130/386 (33.7) 54/235 (23.0)**	**1.5 (1.1 to 1.9)**	**0.11 (0.04 to 0.18)**
Mild paresthesia	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**169/514 (32.9) 54/235 (23.0)**	**1.4 (1.1 to 1.9)**	**0.10 (0.03 to 0.17)**
Moderate anorexia	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**23/386 (6.0) 4/235 (1.7)**	**3.5 (1.2 to 10.0)**	**0.04 (0.01 to 0.07)**
Moderate anorexia	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**22/514 (4.3) 4/235 (1.7)**	**2.5 (0.9 to 7.2)**	**0.03 (0.00 to 0.05)**
Moderate nausea	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**36/514 (7.0) 7/235 (3.0)**	**2.4 (1.1 to 5.2)**	**0.04 (0.01 to 0.07)**
Mood problems	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**23/386 (6.0) 6/235 (2.6)**	**2.3 (1.0 to 5.6)**	**0.03 (0.00 to 0.07)**
Mood problems	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**28/514 (5.4) 6/235 (2.6)**	**2.1 (0.9 to 5.1)**	**0.03 (0.00 to 0.06)**
Nausea	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**16/386 (4.1) 2/235 (0.9)**	**4.9 (1.1 to 21.0)**	**0.03 (0.01 to 0.06)**
Nausea	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**51/235 (21.7) 21/386 (5.4)**	**4.0 (2.5 to 6.5)**	**0.16 (0.11 to 0.22)**
Nausea	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**73/235 (31.1) 21/514 (4.1)**	**7.6 (4.8 to 12.0)**	**0.27 (0.21 to 0.33)**
Nausea	Adelman, 2008[40] Risk of bias Low	200 vs. 100	8/514 (1.6) 16/386 (4.1)	0.4 (0.2 to 0.9)	-0.03 (-0.05 to 0.00)
Nausea	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**73/386 (18.9) 51/514 (9.9)**	**1.9 (1.4 to 2.7)**	**0.09 (0.04 to 0.14)**

Appendix Table 128. Significant dose response adverse effects with topiramate in adults (continued)

Adverse effect	Reference Risk of Bias	Active vs. Control Daily Dose	Events/Randomized (Rate of Outcome in Active Group) Events/Randomized (Rate of Outcome in Control Group)	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Nausea leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**29/514 (5.6) 9/386 (2.3)**	**2.4 (1.2 to 5.1)**	**0.03 (0.01 to 0.06)**
Paresthesia	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**34/386 (8.8) 11/235 (4.7)**	**1.9 (1.0 to 3.6)**	**0.04 (0.00 to 0.08)**
Paresthesia	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**195/386 (50.5) 83/235 (35.3)**	**1.4 (1.2 to 1.7)**	**0.15 (0.07 to 0.23)**
Paresthesia	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**254/514 (49.4) 83/235 (35.3)**	**1.4 (1.2 to 1.7)**	**0.14 (0.07 to 0.22)**
Paresthesia leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**100 vs. 50**	**31/386 (8.0) 8/235 (3.4)**	**2.4 (1.1 to 5.0)**	**0.05 (0.01 to 0.08)**
Paresthesia leading to withdrawal	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**37/514 (7.2) 8/235 (3.4)**	**2.1 (1.0 to 4.5)**	**0.04 (0.01 to 0.07)**
Pharyngitis	Adelman, 2008[40] Risk of bias Low	200 vs. 50	9/514 (1.8) 11/235 (4.7)	0.4 (0.2 to 0.9)	-0.03 (-0.06 to 0.00)
Pharyngitis	Adelman, 2008[40] Risk of bias Low	200 vs. 100	9/514 (1.8) 22/386 (5.7)	0.3 (0.1 to 0.7)	-0.04 (-0.07 to -0.01)
Pharyngitis	Adelman, 2008[40] Risk of bias Low	200 vs. 100	4/514 (0.8) 12/386 (3.1)	0.3 (0.1 to 0.8)	-0.02 (-0.04 to 0.00)
Taste perversion	Adelman, 2008[40] Risk of bias Low	100 vs. 50	30/386 (7.8) 36/235 (15.3)	0.5 (0.3 to 0.8)	-0.08 (-0.13 to -0.02)
Taste perversion	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**63/514 (12.3) 30/386 (7.8)**	**1.6 (1.0 to 2.4)**	**0.04 (0.01 to 0.08)**
Treatment discontinuation	Adelman, 2008[40] Risk of bias Low	100 vs. 50	146/386 (37.8) 108/235 (46.0)	0.8 (0.7 to 1.0)	-0.08 (-0.16 to 0.00)
Treatment discontinuation	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**149/514 (29.0) 41/235 (17.4)**	**1.7 (1.2 to 2.3)**	**0.12 (0.05 to 0.18)**
Treatment discontinuation	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 100**	**239/514 (46.5) 146/386 (37.8)**	**1.2 (1.0 to 1.4)**	**0.09 (0.02 to 0.15)**
Upper respiratory tract infection	Adelman, 2008[40] Risk of bias Low	200 vs. 100	32/514 (6.2) 42/386 (10.9)	0.6 (0.4 to 0.9)	-0.05 (-0.08 to -0.01)
Weight loss	**Adelman, 2008[40] Risk of bias Low**	**200 vs. 50**	**58/514 (11.3) 13/235 (5.5)**	**2.0 (1.1 to 3.6)**	**0.06 (0.02 to 0.10)**

Bold = significant increase in risk of adverse effects with increasing the dose of topiramate when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D129. Dose response in treatment discontinuation due to bothersome adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[47]

Adverse Effect that Lead to Discontinuation	Daily Doses of Divalproex	Events/Randomized with Larger Dose	Events/Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Abdominal pain	1000 mg vs. 500 mg	1/43	0/45	3.1 (0.1 to 75.0)	0.02 (-0.04 to 0.08)
Abdominal pain	1500 mg vs. 1000 mg	0/44	1/43	0.3 (0.0 to 7.8)	-0.02 (-0.09 to 0.04)
Alopecia	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Alopecia	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Asthenia	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Asthenia	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Back pain	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Back pain	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Constipation	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Constipation	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Depression	1000 mg vs. 500 mg	3/43	0/45	7.3 (0.4 to 137.6)	0.07 (-0.02 to 0.16)
Depression	1500 mg vs. 1000 mg	0/44	3/43	0.1 (0.0 to 2.6)	-0.07 (-0.16 to 0.02)
Diarrhea	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Diarrhea	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Emotional liability	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Emotional liability	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Nausea	1000 mg vs. 500 mg	1/43	1/45	1.0 (0.1 to 16.2)	0.00 (-0.06 to 0.06)
Nausea	1500 mg vs. 500 mg	4/44	1/45	4.1 (0.5 to 35.2)	0.07 (-0.03 to 0.16)

Appendix Table D129. Dose response in treatment discontinuation due to bothersome adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial (continued)

Adverse Effect that Lead to Discontinuation	Daily Doses of Divalproex	Events/Randomized with Larger Dose	Events/Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Nausea	1500 mg vs. 1000 mg	4/44	1/43	3.9 (0.5 to 33.6)	0.07 (-0.03 to 0.16)
Pharyngitis	1000 mg vs. 500 mg	1/43	0/45	3.1 (0.1 to 75.0)	0.02 (-0.04 to 0.08)
Pharyngitis	1500 mg vs. 1000 mg	0/44	1/43	0.3 (0.0 to 7.8)	-0.02 (-0.09 to 0.04)
Pneumonia	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Pneumonia	1500 mg vs. 500 mg	0/44	1/45	0.3 (0.0 to 8.1)	-0.02 (-0.08 to 0.04)
Somnolence	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Somnolence	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Thinking abnormal	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Thinking abnormal	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Vomiting	1000 mg vs. 500 mg	0/43	1/45	0.3 (0.0 to 8.3)	-0.02 (-0.08 to 0.04)
Vomiting	1500 mg vs. 500 mg	1/44	1/45	1.0 (0.1 to 15.8)	0.00 (-0.06 to 0.06)
Vomiting	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)
Weight gain	1500 mg vs. 500 mg	1/44	0/45	3.1 (0.1 to 73.3)	0.02 (-0.04 to 0.08)
Weight gain	1500 mg vs. 1000 mg	1/44	0/43	2.9 (0.1 to 70.1)	0.02 (-0.04 to 0.08)

CI = confidence interval
Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

Appendix Table D130. Dose response in adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[47]

Adverse Effect	Daily Doses of Divalproex	Events/ Randomized with Larger Dose	Events/ Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI	Attributable Events per 1000 Treated (95% CI)
Asthenia	1000 mg vs. 500 mg	4/43	4/45	1.0 (0.3 to 3.9)	0.00 (-0.12 to 0.12)	NS
Asthenia	1500 mg vs. 500 mg	10/44	4/45	2.6 (0.9 to 7.5)	0.14 (-0.01 to 0.29)	NS
Asthenia	1500 mg vs. 1000 mg	10/44	4/43	2.4 (0.8 to 7.2)	0.13 (-0.02 to 0.29)	NS
Back pain	1000 mg vs. 500 mg	2/43	3/45	0.7 (0.1 to 4.0)	-0.02 (-0.12 to 0.08)	NS
Back pain	1500 mg vs. 500 mg	6/44	3/45	2.0 (0.5 to 7.7)	0.07 (-0.06 to 0.19)	NS
Back pain	1500 mg vs. 1000 mg	6/44	2/43	2.9 (0.6 to 13.7)	0.09 (-0.03 to 0.21)	NS
Diarrhea	1000 mg vs. 500 mg	2/43	3/45	0.7 (0.1 to 4.0)	-0.02 (-0.12 to 0.08)	NS
Diarrhea	1500 mg vs. 500 mg	8/44	3/45	2.7 (0.8 to 9.6)	0.12 (-0.02 to 0.25)	NS
Diarrhea	**1500 mg vs. 1000 mg**	**8/44**	**2/43**	**3.9 (0.9 to 17.4)**	**0.14 (0.01 to 0.27)**	**135 (5 to 265)**
Dizziness	1000 mg vs. 500 mg	3/43	3/45	1.0 (0.2 to 4.9)	0.00 (-0.10 to 0.11)	NS
Dizziness	1500 mg vs. 500 mg	9/44	3/45	3.1 (0.9 to 10.6)	0.14 (0.00 to 0.28)	NS
Dizziness	1500 mg vs. 1000 mg	9/44	3/43	2.9 (0.9 to 10.1)	0.13 (-0.01 to 0.28)	NS
Dyspepsia	1000 mg vs. 500 mg	8/43	3/45	2.8 (0.8 to 9.8)	0.12 (-0.02 to 0.26)	NS
Dyspepsia	1500 mg vs. 500 mg	7/44	3/45	2.4 (0.7 to 8.6)	0.09 (-0.04 to 0.22)	NS
Dyspepsia	1500 mg vs. 1000 mg	7/44	8/43	0.9 (0.3 to 2.2)	-0.03 (-0.19 to 0.13)	NS
Infection	1000 mg vs. 500 mg	7/43	8/45	0.9 (0.4 to 2.3)	-0.01 (-0.17 to 0.14)	NS
Infection	1500 mg vs. 500 mg	9/44	8/45	1.2 (0.5 to 2.7)	0.03 (-0.14 to 0.19)	NS
Infection	1500 mg vs. 1000 mg	9/44	7/43	1.3 (0.5 to 3.1)	0.04 (-0.12 to 0.20)	NS

Appendix Table 130. Dose response in adverse effects with divalproex for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial (continued)

Adverse Effect	Daily Doses of Divalproex	Events/ Randomized with Larger Dose	Events/ Randomized with Smaller Dose	Relative Risk (95% CI)	Absolute Risk Difference (95% CI	Attributable Events per 1000 Treated (95% CI)
Nausea	**1000 mg vs. 500 mg**	**4/43**	**12/45**	**0.3 (0.1 to 1.0)**	**-0.17 (-0.33 to -0.02)**	**-174 (-329 to -18)**
Nausea	1500 mg vs. 500 mg	15/44	12/45	1.3 (0.7 to 2.4)	0.07 (-0.12 to 0.26)	NS
Nausea	**1500 mg vs. 1000 mg**	**15/44**	**4/43**	**3.7 (1.3 to 10.2)**	**0.25 (0.08 to 0.41)**	**248 (83 to 413)**
Pain	1000 mg vs. 500 mg	3/43	4/45	0.8 (0.2 to 3.3)	-0.02 (-0.13 to 0.09)	NS
Pain	1500 mg vs. 500 mg	5/44	4/45	1.3 (0.4 to 4.5)	0.02 (-0.10 to 0.15)	NS
Pain	1500 mg vs. 1000 mg	5/44	3/43	1.6 (0.4 to 6.4)	0.04 (-0.08 to 0.16)	NS
Somnolence	1000 mg vs. 500 mg	3/43	3/45	1.0 (0.2 to 4.9)	0.00 (-0.10 to 0.11)	NS
Somnolence	1500 mg vs. 500 mg	8/44	3/45	2.7 (0.8 to 9.6)	0.12 (-0.02 to 0.25)	NS
Somnolence	1500 mg vs. 1000 mg	8/44	3/43	2.6 (0.7 to 9.2)	0.11 (-0.03 to 0.25)	NS
Tremor	1000 mg vs. 500 mg	3/43	0/45	7.3 (0.4 to 137.6)	0.07 (-0.02 to 0.16)	NS
Tremor	**1500 mg vs. 500 mg**	**7/44**	**0/45**	**15.3 (0.9 to 260.6)**	**0.16 (0.05 to 0.27)**	**159 (46 to 272)**
Tremor	1500 mg vs. 1000 mg	7/44	3/43	2.3 (0.6 to 8.2)	0.09 (-0.04 to 0.22)	NS
Vomiting	1000 mg vs. 500 mg	2/43	2/45	1.0 (0.2 to 7.1)	0.00 (-0.09 to 0.09)	NS
Vomiting	1500 mg vs. 500 mg	5/44	2/45	2.6 (0.5 to 12.5)	0.07 (-0.04 to 0.18)	NS
Vomiting	1500 mg vs. 1000 mg	5/44	2/43	2.4 (0.5 to 11.9)	0.07 (-0.05 to 0.18)	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D131. Adverse effects with valproate vs. placebo for migraine prevention in adults, results from medium risk of bias randomized controlled clinical trials

Adverse Effects	Daily Dose	Reference	Events/ Randomized with Valproate	Events/ Randomized Placebo	Rate,% with Valproate [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Abdominal pain	1000mg to 1500 mg per day	Jensen, 1994[49]	2/43	1/43	4.7[2.3]	2.0 (0.2 to 21.2)	0.02 (-0.05 to 0.10)
Constipation	400 mg twice a day	Hering, 1992[48]	0/32	1/32	0.0[3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Diarrhea	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Dizziness	400 mg twice a day	Hering, 1992[48]	0/32	1/32	0.0[3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Drowsiness	1000mg to 1500 mg per day	Jensen, 1994[49]	5/43	2/43	11.6[4.7]	2.5 (0.5 to 12.2)	0.07 (-0.04 to 0.18)
Dry mouth	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Dyspepsia	400 mg twice a day	Hering, 1992[48]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Dyspnea	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Increased appetite	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	1/43	2.3[2.3]	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)
Mild weariness	400 mg twice a day	Hering, 1992[48]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Nausea	1000mg to 1500 mg per day	Jensen, 1994[49]	5/43	2/43	11.6[4.7]	2.5 (0.5 to 12.2)	0.07 (-0.04 to 0.18)
Nausea	400 mg twice a day	Hering, 1992[48]	2/32	0/32	6.3[0.0]	5.0 (0.2 to 100.2)	0.06 (-0.04 to 0.16)
Pain in neck/shoulders	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Restless legs	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Tinnitus	1000mg to 1500 mg per day	Jensen, 1994[49]	0/43	1/43	0.0[2.3]	0.3 (0.0 to 8.0)	-0.02 (-0.09 to 0.04)
Total	1000mg to 1500 mg per day	Jensen, 1994[49]	14/43	7/43	32.6[16.3]	2.0 (0.9 to 4.5)	0.16 (-0.02 to 0.34)
Tremor	1000mg to 1500 mg per day	Jensen, 1994[49]	1/43	0/43	2.3[0.0]	3.0 (0.1 to 71.7)	0.02 (-0.04 to 0.09)
Vertigo	1000mg to 1500 mg per day	Jensen, 1994[49]	3/43	0/43	7.0[0.0]	7.0 (0.4 to 131.6)	0.07 (-0.02 to 0.16)
Weight gain	1000mg to 1500 mg per day	Jensen, 1994[49]	3/43	1/43	7.0[2.3]	3.0 (0.3 to 27.7)	0.05 (-0.04 to 0.13)

CI = confidence interval

Appendix Table D132. Adverse effects with propranolol vs. placebo, pooled results from randomized controlled clinical trials (random effects model)

Definition of the Outcome	Sample	Rate with Drug [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Any adverse effects[50, 60, 61, 64]	**414**	**28.4 [17.0]**	**1.7 (1.1 to 2.8)**	**0.09 (0.01 to 0.17)**	**11 (6 to 111)**	**88 (9 to 167)**
Paresthesia[43, 52]	273	10.3 [4.5]	2.1 (0.7 to 6.3)	0.04 (-0.02 to 0.10)	NS	NS
Cold extremities[53, 62]	125	6.1 [1.7]	2.7 (0.4 to 17.6)	0.04 (-0.03 to 0.10)	NS	NS
Depression[53, 60, 61, 236]	411	5.3 [2.5]	2.3 (0.3 to 17.2)	0.03 (-0.02 to 0.09)	NS	NS
Diarrhea[53, 236]	**169**	**11.4 [2.5]**	**4.6 (1.0 to 22.3)**	**0.09 (0.01 to 0.16)**	**11 (6 to 71)**	**89 (14 to 164)**
Dreaming, abnormal.[60, 236]	306	4.6 [0.7]	7.8 (0.9 to 66.0)	0.04 (-0.06 to 0.14)	NS	NS
Fatigue[43, 52, 53, 60, 62, 236]	657	21.3 [11.0]	2.1 (0.8 to 5.8)	0.10 (-0.03 to 0.23)	NS	NS
Insomnia[43, 52, 53, 60, 62]	542	9.2 [6.0]	1.4 (0.7 to 2.8)	0.02 (-0.01 to 0.06)	NS	NS
Nausea[43, 52, 53, 60-62, 236]	**694**	**9.3 [3.5]**	**2.3 (1.1 to 4.5)**	**0.04 (0.01 to 0.08)**	**23 (13 to 111)**	**43 (9 to 77)**
Sleepiness[43, 236]	307	14.9 [2.8]	8.5 (2.5 to 29.0)	0.16 (-0.03 to 0.35)	NS	NS
Dizziness[52, 53, 60, 62]	349	5.4 [3.4]	1.6 (0.6 to 4.3)	0.02 (-0.02 to 0.06)	NS	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D133. Adverse effects with timolol 10mg twice a day (results from randomized controlled clinical trials pooled with random effects model)

Outcome; Reference	Sample	Rate with Timolol [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Attributable Events per 1000 Treated (95% CI)
Total adverse effects[60, 61]	**183**	**38.0 [23.1]**	**1.9 (1.0 to 3.8)**	**0.14 (0.00 to 0.28)**	**137 (0 to 275)**
Dizziness[60, 79]	238	5.6 [3.2]	1.8 (0.5 to 7.1)	0.03 (-0.02 to 0.08)	NS
Tiredness[60, 61, 79]	277	16.1 [9.8]	1.4 (0.7 to 3.0)	0.04 (-0.03 to 0.11)	NS
Insomnia[60, 79]	238	7.7 [3.2]	3.1 (0.8 to 11.6)	0.05 (-0.03 to 0.13)	NS
Nausea[60, 61]	182	1.7 [2.5]	0.5 (0.1 to 3.7)	-0.01 (-0.05 to 0.04)	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D134. Adverse effects with timolol 10mg twice a day (results from randomized controlled clinical trials)

Adverse Effects	Reference Risk of Bias	Events/Randomized with Active Drug	Events/Randomized with Placebo	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Abnormal dreaming	Tfelt-Hansen, 1984[60] Medium	2/96	0/96	5.0 (0.2 to 102.8)	0.02 (-0.01 to 0.06)
Blurred vision	Standnes, 1982[61] Medium	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Cold extremities	Standnes, 1982[61] Medium	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Depression	Tfelt-Hansen, 1984[60] Medium	2/96	0/96	5.0 (0.2 to 102.8)	0.02 (-0.01 to 0.06)
Dyspnea	Standnes, 1982[61] Medium	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Fatigue/tiredness	Tfelt-Hansen, 1984[60] Medium	18/96	8/48	1.1 (0.5 to 2.5)	0.02 (-0.11 to 0.15)
Gastroenteritis	Standnes, 1982[61] Medium	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Increased weight	Standnes, 1982[61] Medium	1/25	0/25	3.0 (0.1 to 70.3)	0.04 (-0.06 to 0.14)
Sleep disturbances	Tfelt-Hansen, 1984[60] Medium	4/96	1/48	2.0 (0.2 to 17.4)	0.02 (-0.04 to 0.08)
Tiredness	Standnes, 1982[61] Medium	6/25	2/13	1.6 (0.4 to 6.7)	0.09 (-0.17 to 0.34)

Appendix Table D 135. Treatment discontinuation due to adverse effects with off label migraine preventive drugs vs. placebo, pooled with random effects model results from randomized controlled clinical trials

Active Drug	Reference	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
Amitriptyline	Couch, 2011[111]	23/194	13/197	1.8 (0.9 to 3.4)	85.8	0.05 (-0.01 to 0.11)	70.37	0.09 (-0.01 to 0.19)	77.17
Amitriptyline	Couch, 1979[103]	5/55	2/61	2.8 (0.6 to 13.7)	14.2	0.06 (-0.03 to 0.15)	29.63	0.12 (-0.06 to 0.31)	22.83
Amitriptyline	Pooled	28/249	15/258	1.9 (1.0 to 3.5)	100	0.05 (0.01 to 0.10)	100	0.10 (0.01 to 0.19)	100
Clonidine	Boisen, 1978[146]	2/71	0/71	5.0 (0.2 to 102.3)	38.41	0.03 (-0.02 to 0.08)	36.3	0.17 (0.00 to 0.33)	44.23
Clonidine	Adam. 1978[148]	2/96	1/96	2.0 (0.2 to 21.7)	61.59	0.01 (-0.03 to 0.05)	63.7	0.04 (-0.10 to 0.18)	55.77
Clonidine	Pooled	4/167	1/167	2.8 (0.4 to 18.5)	100	0.02 (-0.01 to 0.05)	100	0.10 (-0.02 to 0.22)	100
Femoxetine	Orholm, 1986[113]	4/31	2/34	2.2 (0.4 to 11.2)	52.65	0.07 (-0.07 to 0.21)	50.09	0.12 (-0.12 to 0.37)	52.37
Femoxetine	Orholm, 1985[115]	3/29	2/30	1.6 (0.3 to 8.6)	47.35	0.04 (-0.11 to 0.18)	49.91	0.07 (-0.19 to 0.32)	47.63
Femoxetine	Pooled	7/60	4/64	1.9 (0.6 to 6.1)	100	0.05 (-0.05 to 0.15)	100	0.10 (-0.08 to 0.27)	100
Gabapentin	NCT00742209[192]	13/62	2/20	2.1 (0.5 to 8.5)	31.39	0.11 (-0.06 to 0.28)	21.89	0.18 (-0.07 to 0.43)	26.43
Gabapentin	Mathew, 2001[81]	16/98	4/45	1.8 (0.7 to 5.2)	57.25	0.07 (-0.04 to 0.19)	49.16	0.11 (-0.06 to 0.29)	53.91
Gabapentin	Wessely, 1987[84]	2/23	1/22	1.9 (0.2 to 19.6)	11.36	0.04 (-0.10 to 0.19)	28.95	0.08 (-0.21 to 0.38)	19.66
Gabapentin	Pooled	31/183	7/87	1.9 (0.9 to 4.2)	100	0.07 (-0.01 to 0.15)	100	0.13 (0.00 to 0.26)	100
Lamotrigine	Steiner, 1997[87]	7/18	3/40	5.2 (1.5 to 17.8)	54.39	0.31 (0.07 to 0.55)	43.22	0.40 (0.12 to 0.67)	46.23
Lamotrigine	Gupta, 2007[44]	3/60	3/60	1.0 (0.2 to 4.8)	45.61	0.00 (-0.08 to 0.08)	56.78	0.00 (-0.18 to 0.18)	53.77
Lamotrigine	Pooled	10/78	6/100	2.4 (0.5 to 12.2)	100	0.14 (-0.17 to 0.44)	100	0.18 (-0.20 to 0.57)	100
Magnesium	Pfaffenrath, 1996[194]	3/35	1/34	2.9 (0.3 to 26.7)	63.69	0.06 (-0.05 to 0.17)	39.24	0.13 (-0.11 to 0.36)	46.09

Appendix Table D135. Treatment discontinuation due to adverse effects with off label migraine preventive drugs vs. placebo, pooled with random effects model results from individual randomized controlled clinical trials (continued)

Active Drug	Reference	Events/ Randomized with Drug	Events/ Randomized with Placebo	Relative Risk (95% CI)	Relative Risk Weight (Inverse Variance)	Absolute Risk Difference (95% CI)	Absolute Risk Difference Weight (Inverse Variance)	Arcsine Transformed Risk Difference (95% CI)	Arcsine Transformed Risk Difference Weight
Magnesium	Peikert, 1996[195]	3/43	0/38	6.2 (0.3 to 116.4)	36.31	0.07 (-0.02 to 0.16)	60.76	0.27 (0.05 to 0.49)	53.91
Magnesium	Pooled	6/78	1/72	3.8 (0.7 to 22.4)	100	0.06 (0.00 to 0.13)	100	0.20 (0.04 to 0.36)	100
Naproxen sodium	Welch, 1985[237, 238]	2/46	1/46	2.0 (0.2 to 21.3)	64.25	0.02 (-0.05 to 0.09)	45.78	0.06 (-0.14 to 0.27)	53.49
Naproxen sodium	Ziegler, 1985[239]	1/40	0/40	3. 0(0.1 to 71.5)	35.75	0.03 (-0.04 to 0.09)	54.22	0.16 (-0.06 to 0.38)	46.51
Naproxen sodium	Pooled	3/86	1/86	2.3 (0.3 to 15.4)	100	0.02 (-0.03 to 0.07)	100	0.11 (-0.04 to 0.26)	100
Nimodipine	Havanka-Kanniainen, 1985[132]	0/33	1/33	0.3 (0.0 to 7.9)	17.11	-0.03 (-0.11 to 0.05)	66	-0.18 (-0.42 to 0.07)	42.61
Nimodipine	MINES, 1989[133]	3/43	4/46	0.8 (0.2 to 3.4)	82.89	-0.02 (-0.13 to 0.09)	34	-0.03 (-0.24 to 0.18)	57.39
Nimodipine	Pooled	3/76	5/79	0.7 (0.2 to 2.6)	100	-0.03 (-0.09 to 0.04)	100	-0.09 (-0.25 to 0.07)	100

Active Drug	Degree of Freedom	P Value Relative Risk	I Squared Relative Risk	P Value Absolute Risk Difference	I Squared Absolute Risk Difference	P Value, Arcsine Transformed Risk Difference	I Squared, Arcsine Transformed Risk Difference
Amitriptyline	1	0.62	0.00%	0.01	60.30%	0.02	58.40%
Clonidine	1	0.64	0.00%	0.22	32.30%	0.24	26.90%
Femoxetine	1	0.77	0.00%	0.31	4.60%	0.31	2.90%
Gabapentin	2	0.99	0.00%	0.86	0.00%	0.67	0.00%
Lamotrigine	1	0.11	62.00%	0.92	0.00%	0.76	0.00%
Magnesium	1	0.69	0.00%	0.55	0.00%	0.26	22.90%
Naproxen	1	0.84	0.00%	0.75	0.00%	0.76	0.00%
Nimodipine	1	0.62	0.00%	0.83	0.00%	0.87	0.00%

Appendix Table D136. Adverse effects with antiepileptic drugs vs. placebo, pooled results from randomized controlled clinical trials (random effects model)

Drug	Outcome, Reference	Sample	Rate with Drug [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Divalproex	Diarrhea[46, 47]	297	6.6 [3.6]	1.8 (0.6 to 5.2)	0.03 (-0.02 to 0.08)	NS	NS
Divalproex	Asthenia[45-47]	404	17.3 [9.8]	2.1 (0.5 to 9.5)	0.11 (-0.07 to 0.30)	NS	NS
Divalproex	Sleepiness[45-47]	405	15.6 [2.8]	4.9 (1.9 to 13.0)	0.13 (0.00 to 0.26)	NS	NS
Divalproex	**Tremor[45, 47]**	**166**	**14.0 [0.0]**	**8.5 (1.1 to 66.1)**	**0.14 (0.06 to 0.21)**	**7 (5 to 16)**	**137 (64 to 211)**
Divalproex	**Vomiting[45-47]**	**404**	**11.0 [1.4]**	**5.3 (1.5 to 18.4)**	**0.11 (0.02 to 0.20)**	**9 (5 to 63)**	**108 (16 to 200)**
Divalproex	Infection[46, 47]	298	16.2 [14.3]	1.1 (0.6 to 2.0)	0.01 (-0.08 to 0.09)	NS	NS
Divalproex	Nausea[45-47]	403	22.9 [9.5]	2.7 (1.2 to 6.0)	0.13 (-0.04 to 0.29)	NS	NS
Valproate	Nausea[48, 49]	150	9.3 [2.7]	3.2 (0.7 to 14.0)	0.07 (-0.01 to 0.14)	NS	NS
Gabapentin	**Any adverse effects[81, 192]**	**225**	**70.6 [54.4]**	**2.0 (1.1 to 3.6)**	**0.16 (0.02 to 0.30)**	**6 (3 to 56)**	**158 (18 to 297)**
Gabapentin	Weight increase (gain)[81, 192]	321	5.2 [3.8]	1.5 (0.4 to 5.4)	0.01 (-0.03 to 0.06)	NS	NS
Gabapentin	**Dizziness[81, 192]**	**406**	**28.0 [7.5]**	**4.3 (1.4 to 12.9)**	**0.19 (0.05 to 0.34)**	**5 (3 to 20)**	**193 (51 to 335)**
Gabapentin	Infection[81, 192]	225	8.7 [17.8]	0.4 (0.2 to 1.0)	-0.06 (-0.19 to 0.07)	NS	NS
Gabapentin	**Sleepiness[81, 192]**	**225**	**20.6 [7.6]**	**3.3 (1.2 to 8.9)**	**0.13 (0.04 to 0.22)**	**8 (5 to 24)**	**128 (41 to 216)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D137. Adverse effects with acetazolamide, 500 mg/day vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[80]

Adverse effect	Events/ Randomized with Acetazolamide	Events/ Randomized with Placebo	Rate, % with Active Drug [Placebo]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat (95% CI)	Attributable Events (95% CI)
Paresthesia	**21/26**	**2/27**	**80.8 [7.4]**	**10.9 (2.8 to 41.9)**	**0.73 (0.55 to 0.91)**	**1 (1 to 2)**	**734 (553 to 914)**
Fatigue, drowsiness, memory impairment, malaise, fasciculation	**15/26**	**4/27**	**57.7 [14.8]**	**3.9 (1.5 to 10.2)**	**0.43 (0.20 to 0.66)**	**2 (2 to 5)**	**429 (196 to 661)**
Gastrointestinal intolerance	3/26	2/27	11.5 [7.4]	1.6 (0.3 to 8.6)	0.04 (-0.12 to 0.20)	NS	NS
Hypokalemia	1/26	0/27	3.8 [0.0]	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.14)	NS	NS
Hyperuricemia	1/26	0/27	3.8 [0.0]	3.1 (0.1 to 73.1)	0.04 (-0.06 to 0.14)	NS	NS
Skin eruption	0/26	2/27	0.0 [7.4]	0.2 (0.0 to 4.1)	-0.07 (-0.19 to 0.04)	NS	NS
Fever and shivering	0/26	1/27	0.0 [3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)	NS	NS
Dry mouth	1/26	1/27	3.8 [3.7]	1.0 (0.1 to 15.7)	0.00 (-0.10 to 0.10)	NS	NS
Breast tension	0/26	1/27	0.0 [3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)	NS	NS
Rhinitis	1/26	2/27	3.8 [7.4]	0.5 (0.1 to 5.4)	-0.04 (-0.16 to 0.09)	NS	NS
Tinnitus	0/26	1/27	0.0 [3.7]	0.3 (0.0 to 8.1)	-0.04 (-0.13 to 0.06)	NS	NS
Miscellaneous	1/26	3/27	3.8 [11.1]	0.3 (0.0 to 3.1)	-0.07 (-0.21 to 0.07)	NS	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D138. Adverse effects with carbamazepine vs. placebo for migraine prevention in adults, results from medium risk of bias randomized controlled clinical trial[86]

Adverse Effect	Events/ Randomized with Active Drug	Events/ Randomized with Placebo	Rate, % with Active Drug [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)
Drowsiness	**5/48**	**0/48**	**10.4 [0.0]**	**11.0 (0.6 to 193.6)**	**0.10 (0.01 to 0.20)**	**10 (5 to 88)**	**104 (11 to 197)**
Vertigo or giddiness	**23/48**	**2/48**	**47.9 [4.2]**	**11.5 (2.9 to 46.1)**	**0.44 (0.29 to 0.59)**	**2 (2 to 4)**	**438 (285 to 590)**
Total	**30/48**	**11/48**	**62.5 [22.9]**	**2.7 (1.6 to 4.8)**	**0.40 (0.21 to 0.58)**	**3 (2 to 5)**	**396 (214 to 577)**
Necessitating reduction of dosage	**6/48**	**0/48**	**12.5 [0.0]**	**13.0 (0.8 to 224.5)**	**0.13 (0.03 to 0.22)**	**8 (4 to 39)**	**125 (26 to 224)**
Nausea	4/48	3/48	8.3 [6.3]	1.3 (0.3 to 5.6)	0.02 (-0.08 to 0.12)	NS	NS
Dry mouth	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)	NS	NS
Heavy eyes	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)	NS	NS
Constipation	2/48	0/48	4.2 [0.0]	5.0 (0.2 to 101.5)	0.04 (-0.03 to 0.11)	NS	NS
Vomiting	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)	NS	NS
Weight gain	1/48	1/48	2.1 [2.1]	1.0 (0.1 to 15.5)	0.00 (-0.06 to 0.06)	NS	NS
Sweating	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)	NS	NS
Transient rash	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)	NS	NS
Dysuria	1/48	0/48	2.1 [0.0]	3.0 (0.1 to 71.9)	0.02 (-0.04 to 0.08)	NS	NS
Blacked nose	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)	NS	NS
Lack of drive	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)	NS	NS
Flushing	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)	NS	NS
Blunted feeling	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)	NS	NS
Heavy head	0/48	1/48	0.0 [2.1]	0.3 (0.0 to 8.0)	-0.02 (-0.08 to 0.04)	NS	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D139. Adverse effects with gabapentin, titrated up to 2400 mg daily vs. placebo for migraine prevention in adults, results from medium risk of bias randomized controlled clinical trial[81]

Adverse Effect	Events/ Randomized with Active Drug	Events/ Randomized with Placebo	Rate, % with Active Drug [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)
Dizziness	**25/98**	**5/98**	**25.5 [11.1]**	**2.3 (0.9 to 5.6)**	**0.14 (0.02 to 0.27)**	**7 (4 to 56)**	**144 (18 to 270)**
Somnolence	**24/98**	**5/98**	**24.5 [11.1]**	**2.2 (0.9 to 5.4)**	**0.13 (0.01 to 0.26)**	**7 (4 to 117)**	**134 (9 to 259)**
Asthenia	22/98	12/98	22.4 [26.7]	0.8 (0.5 to 1.5)	-0.04 (-0.20 to 0.11)	NS	NS
Infection	11/98	11/98	11.2 [24.4]	0.5 (0.2 to 1.0)	-0.13 (-0.27 to 0.01)	NS	NS
Weight gain	3/98	1/98	3.1 [2.2]	1.4 (0.1 to 12.9)	0.01 (-0.05 to 0.06)	NS	NS
Designated as probably, possibly, or definitely related to study drug (Total)	**66/98**	**22/98**	**67.3 [48.9]**	**1.4 (1.0 to 1.9)**	**0.18 (0.01 to 0.36)**	**5 (3 to 87)**	**185 (12 to 358)**

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level ;NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D140. Treatment discontinuation due to bothersome adverse effects with lamotrigine, titrated up to 200 mg daily vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[87]

Adverse Effect	Events/ Randomized with Active Drug	Events/ Randomized with Placebo	Rate, % with Active Drug [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)
Rash	**7/18**	**1/40**	**38.9 [3]**	**15.6 (2.1 to 117.3)**	**0.36 (0.13 to 0.59)**	**3 (2 to 7)**	**364 (134 to 594)**
Dizziness	1/18	0/40	5.6 [0]	6.5 (0.3 to 151.7)	0.06 (-0.07 to 0.18)	NS	NS
Leucopenia	0/18	1/40	0.0 [3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)	NS	NS
Dyspepsia	0/18	1/40	0.0 [3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)	NS	NS
Nausea	0/18	1/40	0.0 [3]	0.7 (0.0 to 16.9)	-0.03 (-0.12 to 0.07)	NS	NS
Other	2/18	1/40	11.1 [3]	4.4 (0.4 to 45.9)	0.09 (-0.07 to 0.24)	NS	NS
Any	**7/18**	**3/40**	**38.9 [8]**	**5.2 (1.5 to 17.8)**	**0.31 (0.07 to 0.55)**	**3 (2 to 13)**	**314 (74 to 553)**

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level;NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D141. Adverse effects with oxcarbazepine, titrated to a maximum tolerated dose of 1,200 mg/day vs. placebo for migraine prevention in adults, results from low risk of bias randomized controlled clinical trial[83]

Adverse Effect	Events/ Randomized with Active Drug	Events/ Randomized with Placebo	Rate, % with Active Drug [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)
Patients with any adverse effects	**68/85**	**55/85**	**80.0 [64.7]**	**1.2 (1.0 to 1.5)**	**0.15 (0.02 to 0.29)**	**7 (4 to 49)**	**153 (20 to 285)**
Fatigue	**17/85**	**6/85**	**20.0 [7.1]**	**2.8 (1.2 to 6.8)**	**0.13 (0.03 to 0.23)**	**8 (4 to 35)**	**129 (28 to 230)**
Dizziness	**15/85**	**6/85**	**17.6 [7.1]**	**2.5 (1.0 to 6.1)**	**0.11 (0.01 to 0.20)**	**9 (5 to 121)**	**106 (8 to 204)**
Nausea	**14/85**	**4/85**	**16.5 [4.7]**	**3.5 (1.2 to 10.2)**	**0.12 (0.03 to 0.21)**	**8 (5 to 37)**	**118 (27 to 208)**
Somnolence	7/85	6/85	8.2 [7.1]	1.2 (0.4 to 3.3)	0.01 (-0.07 to 0.09)	NS	NS
Balance disorder	5/85	2/85	5.9 [2.4]	2.5 (0.5 to 12.5)	0.04 (-0.02 to 0.09)	NS	NS
Insomnia	5/85	6/85	5.9 [7.1]	0.8 (0.3 to 2.6)	-0.01 (-0.09 to 0.06)	NS	NS
Migraine	5/85	2/85	5.9 [2.4]	2.5 (0.5 to 12.5)	0.04 (-0.02 to 0.09)	NS	NS
Paresthesia	5/85	1/85	5.9 [1.2]	5.0 (0.6 to 41.9)	0.05 (-0.01 to 0.10)	NS	NS
Sinusitis	2/85	5/85	2.4 [5.9]	0.4 (0.1 to 2.0)	-0.04 (-0.09 to 0.02)	NS	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence level; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D142. Adverse effects with off label antidepressants vs. placebo, pooled results from randomized controlled clinical trials (random effects model)

Active Drug	Outcome, Reference	Sample	Rate with Drug [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Amitriptyline	**Total adverse effects[104, 111]**	**494**	**60.2 [28.8]**	4.0 (2.2 to 7.3)	**0.32 (0.18 to 0.47)**	**3 (2 to 6)**	**322 (175 to 469)**
Amitriptyline	**Dizziness[104, 111]**	**431**	**10.3 [5.1]**	**2.1 (1.0 to 4.4)**	**0.05 (0.00 to 0.10)**	**19 (10 to 500)**	**52 (2 to 102)**
Amitriptyline	Depression [104, 111]	431	2.3 [1.4]	1.7 (0.4 to 7.3)	0.01 (-0.01 to 0.03)	NS	NS
Amitriptyline	Dry mouth[104, 111]	431	32.7 [6.9]	6.6 (3.6 to 12.0)	0.18 (-0.05 to 0.40)	NS	NS
Amitriptyline	**Drowsiness[104, 111]**	**431**	**27.1 [9.2]**	**3.6 (2.1 to 6.3)**	**0.18 (0.11 to 0.25)**	**6 (4 to 9)**	**180 (109 to 251)**
Amitriptyline	Weight increase (gain)[104, 111]		1.9 [1.8]	1.0 (0.2 to 4.4)	0.00 (-0.02 to 0.03)		
Amitriptyline	**Constipation[104, 111]**	**431**	**11.2 [3.7]**	**3.2 (1.4 to 7.1)**	**0.07 (0.03 to 0.12)**	**14 (8 to 40)**	**74 (25 to 123)**
Amitriptyline	Nausea[104, 111]	431	2.8 [2.3]	1.2 (0.4 to 4.1)	0.01 (-0.02 to 0.03)	NS	NS
Femoxetine	**Adverse events: Any[113, 114]**	**124**	**23.0 [6.3]**	**4.4 (1.3 to 14.6)**	**0.17 (0.05 to 0.29)**	**6 (3 to 21)**	**167 (48 to 286)**
Femoxetine	Nausea[113, 114]	124	3.3 [0.0]	3.2 (0.3 to 31.5)	0.03 (-0.03 to 0.09)	NS	NS
Fluoxetine	**Adverse events[116, 117, 119]**	**195**	**56.9 [45.3]**	**2.1 (1.0 to 4.2)**	**0.12 (0.01 to 0.24)**	**8 (4 to 200)**	**121 (5 to 238)**
Fluoxetine	Insomnia[117, 119]	163	20.4 [15.7]	1.5 (0.6 to 3.4)	0.06 (-0.03 to 0.15)	NS	NS

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D143. Strength of evidence of treatment discontinuation due to adverse effects with beta-blockers for migraine prevention in adults (evidence from randomized controlled clinical trials)

Reference	Drug	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Forssman, 1982[95] Forssman, 1983[96]	Atenolol	Medium	Yes	Not applicable	No	Low
van de Ven, 1997[101]	Bisoprolol	Medium	Yes	Not applicable	No	Low
Andersson, 1983[97]	Metoprolol	Medium	Yes	Not applicable	No	Low
Freitag, 1984[98]	Nadolol	Low	Yes	Not applicable	No	Low
Sjaastad, 1972[89]	Pindolol (LB-46)	Medium	Yes	Not applicable	No	Low

Appendix Table D144. Treatment discontinuation due to adverse effects with beta-blockers for migraine prevention in adults, results from individual randomized controlled clinical trials

Reference Risk of Bias	Drug and Dose	Outcome	Events/ Randomized [Rate of Outcome with Drug, %]	Events/ Randomized [Rate of Outcome with Placebo, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Johannsson, 1987[99] Medium	Atenolol 100mg	Withdrawal due to side effects	0/72 [0.0%]	3/72 [4.2%]	0.1 (0.0 to 2.7)	-0.04 (-0.09 to 0.0)
Forssman, 1982[95] Forssman, 1983[96] Medium	Atenolol 100mg/day	Withdrawal due to mood alternations and increased tiredness	1/24 [4.2%]	0/24 [0.0%]	3.0 (0.1 to 70.2)	0.04 (-0.07 to 0.1)
Forssman, 1982[95] Forssman, 1983[96] Medium	Atenolol 100mg/day	Withdrawal due to intolerable increase of headache attack	0/24 [0.0%]	1/24 [4.2%]	0.3 (0.0 to 7.8)	-0.04 (-0.15 to 0.1)
van de Ven, 1997[101] Medium	Bisoprolol 5mg/day	Dropped out of the study due to adverse effects	4/74 [5.4%]	2/37 [5.3%]	1.0 (0.2 to 5.2)	0.00 (-0.09 to 0.1)
	Bisoprolol 10mg/day		7/77 [9.1%]	2/38 [5.3%]	1.7 (0.4 to 7.9)	0.04 (-0.06 to 0.1)
Andersson, 1983[97] Medium	Metoprolol 200mg/day thereafter	Discontinued due to side-effects	1/34 [2.9%]	1/37 [2.7%]	1.1 (0.1 to 16.7)	0.00 (-0.07 to 0.1)
Freitag, 1984[98] Low	Nadolol 80mg to 240mg/day	Discontinued due to bradycardia	1/24 [4.2%]	0/8 [0.0%]	1.1 (0.0 to 24.2)	0.04 (-0.13 to 0.2)
Sjaastad, 1972[89] Medium	Pindolol (LB-46) 7.5 to 15mg	Discontinued due to side-effects	3/28 [10.7%]	0/28 [0.0%]	7.0 (0.4 to 129.5)	0.11 (-0.02 to 0.2)

Appendix Table D145. Adverse effects with beta-blockers for migraine prevention in adults (results from randomized controlled clinical trials)

Active Drug	Outcome, Reference	Sample	Rate with Drug [Placebo]	Odds Ratio (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Atenolol	Tiredness, diffuse[62, 95]	118	5.1 [0.0]	4.2 (0.4 to 38.8)	0.04 (-0.02 to 0.11)	NS	NS
Metoprolol	**Fatigue[97, 102]**	**91**	**18.2 [4.3]**	**4.6 (0.9 to 24.4)**	**0.14 (0.02 to 0.27)**	**7 (4 to 67)**	**141 (15 to 268)**
Metoprolol	**Sleep disturbances[97, 100]**	**225**	**9.9 [4.4]**	**2.3 (0.6 to 9.1)**	**0.05 (0.00 to 0.11)**	**19 (9 to 1000)**	**54 (1 to 106)**
Metoprolol	Gastrointestinal disturbances[97, 102]	91	2.3 [12.8]	0.2 (0.0 to 1.3)	-0.10 (-0.20 to 0.01)	NS	NS

Bold = significant differences at 95% CI when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D146. Comparative safety of topiramate vs. onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials)

Adverse Effects	Reference Risk of Bias	Events/ Randomized with Topiramate	Events/ Randomized with Onabotulinumtoxin A	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Nausea	Cady, 2011[163] Medium	6/30	13/29	0.4 (0.2 to 1.0)	**-0.25 (-0.48 to -0.02)**
Mood swing	Cady, 2011[163] Medium	6/30	4/29	1.5 (0.5 to 4.6)	0.06 (-0.13 to 0.25)
Difficulty concentrating or with memory	Cady, 2011[163] Medium	11/30	13/29	0.8 (0.4 to 1.5)	-0.08 (-0.33 to 0.17)
Mild fatigue	Cady, 2011[163] Medium	15/30	16/29	0.9 (0.6 to 1.5)	-0.05 (-0.31 to 0.20)
Cognitive deficits (probable)	Mathew, 2009[161] High	0/30	0/30	0.0 (0.0 to 0.0)	0.00 (0.00 to 0.00)
Dry mouth/thirst (definite)	Mathew, 2009[161] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Sleepiness/tiredness/fatigue/dizziness (probable)	Mathew, 2009[161] High	1/30	1/30	1.0 (0.1 to 15.3)	0.00 (-0.09 to 0.09)
Depression/mood disturbance (probable)	Mathew, 2009[161] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Appetite/weight loss (probable)	Mathew, 2009[161] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Night sweats (probable)	Mathew, 2009[161] High	1/30	0/30	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Night sweats (definite)	Mathew, 2009[161] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Blurred vision/vision problems (definite)	Mathew, 2009[161] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Blurred vision/vision problems (probable)	Mathew, 2009[161] High	2/30	0/30	5.0 (0.3 to 100.0)	0.07 (-0.04 to 0.17)
Sleepiness/tiredness/fatigue/dizziness (definite)	Mathew, 2009[161] High	3/30	2/30	1.5 (0.3 to 8.3)	0.03 (-0.11 to 0.17)
Dry mouth/thirst (probable)	Mathew, 2009[161] High	3/30	0/30	7.0 (0.4 to 129.9)	0.10 (-0.02 to 0.22)
Depression/mood disturbance (definite)	Mathew, 2009[161] High	5/30	0/30	11.0 (0.6 to 190.5)	**0.17 (0.03 to 0.31)**
Appetite/weight loss (definite)	**Mathew, 2009[161] High**	**8/30**	**0/30**	**17.0 (1.0 to 281.9)**	**0.27 (0.10 to 0.43)**
Paresthesia (probable)	**Mathew, 2009[161] High**	**11/30**	**0/30**	**23.0 (1.4 to 373.5)**	**0.37 (0.19 to 0.54)**

Appendix Table D146. Comparative safety of topiramate vs. onabotulinumtoxin A for migraine prevention in adults (results from individual randomized controlled clinical trials) (continued)

Adverse Effects	Reference Risk of Bias	Events/ Randomized with Topiramate	Events/ Randomized with Onabotulinumtoxin A	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Paresthesia (definite)	**Mathew, 2009[161] High**	**14/30**	**3/30**	**4.7 (1.5 to 14.6)**	**0.37 (0.16 to 0.57)**
Cognitive deficits (definite)	**Mathew, 2009[161] High**	**15/30**	**0/30**	**31.0 (1.9 to 495.6)**	**0.50 (0.32 to 0.68)**
Drug-related adverse effects	**Mathew, 2009[161] High**	**25/30**	**18/30**	**1.4 (1.0 to 1.9)**	**0.23 (0.01 to 0.45)**
Probable/possible drug-related	Mathew, 2009[161] High	26/30	22/30	1.2 (0.9 to 1.5)	0.13 (-0.07 to 0.33)
All adverse effects	Mathew, 2009[161] High	28/30	26/30	1.1 (0.9 to 1.3)	0.07 (-0.08 to 0.22)

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D147. Comparative safety of divalproex sodium vs. onabotulinumtoxin A for migraine prevention in adults (results from a single medium risk of bias randomized controlled clinical trial)[164]

Adverse Effect	Events/ Randomized with Divalproex	Events/ Randomized with Onabotulinumtoxin A	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Ptosis, eyelid (possibly related to treatment)	**0/29**	**8/30**	0.1 (0.0 to 1.0)	**-0.27 (-0.43 to -0.10)**
Ptosis, eyebrow (possibly related to treatment)	**0/29**	**5/30**	0.1 (0.0 to 1.6)	**-0.17 (-0.31 to -0.02)**
Headache intensity/frequency increase (possibly related to treatment)	0/29	2/30	0.2 (0.0 to 4.1)	-0.07 (-0.17 to 0.04)
Vision disturbance (possibly related to treatment)	2/29	1/30	2.1 (0.2 to 21.6)	0.04 (-0.08 to 0.15)
Dizziness (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Infection, viral (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Numbness (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Pruritis (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Tinnitus (possibly related to treatment)	2/29	0/30	5.2 (0.3 to 103.2)	0.07 (-0.04 to 0.18)
Tremors (possibly related to treatment)	3/29	0/30	7.2 (0.4 to 134.2)	0.10 (-0.02 to 0.23)
Other gastrointestinal discomfort (possibly related to treatment)	3/29	0/30	7.2 (0.4 to 134.2)	0.10 (-0.02 to 0.23)
Sleepiness (possibly related to treatment)	4/29	0/30	9.3 (0.5 to 165.4)	0.14 (0.00 to 0.27)
Weight gain (possibly related to treatment)	4/29	1/30	4.1 (0.5 to 34.9)	0.10 (-0.04 to 0.25)
Fatigue (possibly related to treatment)	5/29	0/30	11.4 (0.7 to 196.7)	**0.17 (0.03 to 0.32)**
Hair loss (possibly related to treatment)	5/29	1/30	5.2 (0.6 to 41.6)	0.14 (-0.01 to 0.29)
Nausea (possibly related to treatment)	**9/29**	**1/30**	**9.3 (1.3 to 68.9)**	**0.28 (0.10 to 0.46)**
Related to treatment adverse effect	18/29	12/30	1.6 (0.9 to 2.6)	0.22 (-0.03 to 0.47)
Possibly related to treatment adverse effect	22/29	15/30	1.5 (1.0 to 2.3)	**0.26 (0.02 to 0.50)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0.
CI = confidence interval

Appendix Table D148. Comparative safety of amitriptyline vs. botulinum toxin type A for migraine prevention in adults (results from a single high risk of bias randomized controlled clinical trial)[162]

Adverse Effect	Events/ Randomized with Amitriptyline	Events/ Randomized with Botulinum	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Constipation	**14/37**	**0/35**	**27.5 (1.7 to 443.8)**	**0.38 (0.22 to 0.54)**
Dry mouth	**16/37**	**5/35**	**3.0 (1.2 to 7.4)**	**0.29 (0.09 to 0.49)**
Somnolence	**19/37**	**1/35**	**18.0 (2.5 to 127.2)**	**0.48 (0.31 to 0.66)**
Weight gain	**22/37**	**4/35**	**5.2 (2.0 to 13.6)**	**0.48 (0.29 to 0.67)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D149. Treatment discontinuation due to adverse effects with migraine preventive drugs compared to each other, results from individual randomized controlled clinical trials

Active vs. Control Drug	Adverse Effect that Resulted in Treatment Discontinuation	Reference Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Topiramate vs. Amitriptyline	Fatigue	Dodick, 2009[172] Risk of bias Low	1.4 (0.4 to 5.0)	0.01 (-0.03 to 0.05)
Topiramate vs. Amitriptyline	Hypesthesia	Dodick, 2009[172] Risk of bias Low	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Topiramate vs. Amitriptyline	Dizziness	Dodick, 2009[172] Risk of bias Low	6.6 (0.3 to 127.7)	0.02 (-0.01 to 0.04)
Topiramate vs. Lamotrigine	Any adverse event	Gupta, 2007[44] Risk of bias Low	1.0 (0.2 to 4.8)	0.00 (-0.08 to 0.08)
Topiramate vs. Histamine	**Any adverse event**	**Millan-Guerrero, 200[169] Risk of bias Low**	**21.0 (1.3 to 347.9)**	**0.22 (0.10 to 0.35)**
Topiramate vs. Levetiracetam	Somnolence (drowsiness) and sedation	de Tommaso, 2007[168] Risk of bias Medium	3.4 (0.2 to 77.6)	0.08 (-0.11 to 0.26)
Propranolol vs. Nadolol	Any adverse event	Sudilovsky, 1987[191] Risk of bias Medium	2.1 (0.4 to 11.1)	0.05 (-0.05 to 0.15)
Amitriptyline vs. Dihydroergotamine	Any adverse event	Bonuso, 1983[159] Risk of bias Medium	1.4 (0.3 to 7.7)	0.04 (-0.16 to 0.24)
Clomipramine vs. Metoprolol	**Severe**	**Langohr, 1985[184] Risk of bias Medium**	**37.0 (2.3 to 600.9)**	**0.29 (0.17 to 0.40)**
Venlafaxine vs. Amitriptyline	Any adverse event	Bulut, 2004[109] Risk of bias Medium	0.2 (0.0 to 1.6)	-0.15 (-0.32 to 0.01)
Metoprolol vs. Bisoprolol	Any adverse event	Worz, 1991[186] Risk of bias Medium	0.6 (0.2 to 1.8)	-0.04 (-0.12 to 0.05)
Metoprolol vs. Nebivolol	Any adverse event	Schellenberg, 2008[189] Risk of bias Medium	1.1 (0.1 to 16.6)	0.01 (-0.17 to 0.19)
Metoprolol vs. Aspirin	Drowsiness	Grotemeyer, 1990[185] Risk of bias Medium	5.0 (0.3 to 99.7)	0.07 (-0.04 to 0.18)
Metoprolol vs. Aspirin	Gastrointestinal side-effects	Grotemeyer, 1990[185] Risk of bias Medium	0.1 (0.0 to 1.6)	**-0.18 (-0.33 to -0.03)**
Metoprolol vs. Clonidine	Discontinued due to adverse event and/or lack of efficacy	Louis, 1985[183] Risk of bias Medium	0.1 (0.0 to 2.0)	-0.13 (-0.26 to 0.00)
Dihydroergocryptine vs. Dihydroergotamine	Gastric pain	Frediani, 1991[240] Risk of bias Medium	0.2 (0.0 to 4.0)	-0.07 (-0.17 to 0.04)
Dihydroergocryptine vs. Dihydroergotamine	Nausea(severe)	Frediani, 1991[240] Risk of bias Medium	0.2 (0.0 to 4.0)	-0.07 (-0.17 to 0.04)

Appendix Table D149. Treatment discontinuation due to adverse effects with migraine preventive drugs compared to each other, results from individual randomized controlled clinical trials (continued)

Active vs. Control Drug	Adverse Effect that Resulted in Treatment Discontinuation	Reference Risk of Bias	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Dihydroergocryptine vs. Dihydroergotamine	Skin rash(severe)	Frediani, 1991[240] Risk of bias Medium	3.0 (0.1 to 70.8)	0.03 (-0.05 to 0.12)
Lisuride vs. Lisuride	Gastric pain and feeling badly	Bisceglia, 1990[241] Risk of bias Medium	0.3 (0.0 to 7.7)	-0.05 (-0.18 to 0.08)
Lisuride vs. Methysergide	Any adverse event	Hermann, 1977[153] Risk of bias Medium	0.4 (0.3 to 0.7)	-0.22 (-0.33 to -0.11)
Lisuride vs. Methysergide	Tiredness	Hermann, 1977[153] Risk of bias Medium	0.1 (0.0 to 2.6)	-0.02 (-0.06 to 0.01)
Lisuride vs. Methysergide	**Dizziness**	**Hermann, 1977[153] Risk of bias Medium**	**0.2 (0.1 to 0.6)**	**-0.11 (-0.17 to -0.04)**
Lisuride vs. Methysergide	Paresthesia	Hermann, 1977[153] Risk of bias Medium	0.2 (0.0 to 1.6)	-0.03 (-0.07 to 0.01)
Lisuride vs. Methysergide	Somnolence (Drowsiness)	Hermann, 1977[153] Risk of bias Medium	0.8 (0.2 to 2.8)	-0.01 (-0.06 to 0.04)
Lisuride vs. Methysergide	Tachycardia	Hermann, 1977[153] Risk of bias Medium	0.1 (0.0 to 1.9)	-0.03 (-0.07 to 0.00)
Lisuride vs. Methysergide	**Vomiting**	**Hermann, 1977[153] Risk of bias Medium**	**0.1 (0.0 to 0.4)**	**-0.13 (-0.20 to -0.07)**
Lisuride vs. Methysergide	Eye pain	Hermann, 1977[153] Risk of bias Medium	0.1 (0.0 to 2.6)	-0.02 (-0.06 to 0.01)
Lisuride vs. Methysergide	Gastro-intestinal	Hermann, 1977[153] Risk of bias Medium	0.6 (0.2 to 1.5)	-0.04 (-0.10 to 0.03)
Lisuride vs. Methysergide	Nausea	Hermann, 1977[153] Risk of bias Medium	0.3 (0.1 to 0.7)	-0.12 (-0.19 to -0.04)
Lisuride vs. Methysergide	Neuralgia	Hermann, 1977[153] Risk of bias Medium	0.1 (0.0 to 1.3)	-0.05 (-0.09 to -0.01)

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D150. Discontinuation due to treatment failure with topiramate versus other drugs for migraine prevention in adults

Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	2/178 [1.1]	0/169 [0.0]	4.7 (0.2 to 98.2)	0.01 (-0.01 to 0.03)
Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	1/60 [1.7]	1/60 [1.7]	1.0 (0.1 to 15.6)	0.00 (-0.05 to 0.05)

CI = confidence interval

Appendix Table D151. Adverse effects with preventive drugs compared to each other, pooled with random effects models results from randomized controlled clinical trials

Active	Control	Definition of the Outcome, References	Sample	% with Active [Control]	Pooled Relative Risk (95% CI)	Pooled Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Metoprolol	Bisoprolol	Adverse events[186, 187]	406	18.2 [22.7]	0.8 (0.5 to 1.2)	-0.04 (-0.12 to 0.04)	NS	NS
Timolol	Propranolol	Adverse events: Total[60, 61]	242	38.0 [33.9]	1.1 (0.8 to 1.6)	0.04 (-0.08 to 0.16)	NS	NS
Propranolol	Femoxetine	Gastric distress[77, 177]	107	1.9 [3.8]	0.6 (0.1 to 4.8)	-0.02 (-0.09 to 0.05)	NS	NS
Propranolol	Femoxetine	Palpitations[77, 177]	107	7.4 [1.9]	3.0 (0.5 to 18.0)	0.05 (-0.03 to 0.13)	NS	NS
Propranolol	Femoxetine	Exanthema[77, 177]	107	7.4 [3.8]	1.9 (0.3 to 10.6)	0.03 (-0.06 to 0.11)	NS	NS
Propranolol	Femoxetine	Dizziness[77, 177]	107	20.4 [7.5]	2.7 (0.9 to 8.1)	0.10 (-0.13 to 0.34)	NS	NS
Propranolol	**Femoxetine**	**Tiredness[77, 177]**	**107**	**31.5 [9.4]**	**3.3 (0.8 to 13.7)**	**0.23 (0.09 to 0.37)**	**4 (3 to 11)**	**230 (87 to 374)**
Propranolol	Femoxetine	Sleep disturbances[77, 177]	107	11.1 [3.8]	2.7 (0.5 to 14.2)	0.06 (-0.08 to 0.19)	NS	NS
Propranolol	Femoxetine	Feeling unwell[77, 177]	107	5.6 [7.5]	0.8 (0.1 to 5.1)	-0.03 (-0.14 to 0.09)	NS	NS
Timolol	Propranolol	Depression[60, 61]	242	1.7 [3.3]	0.6 (0.1 to 2.6)	-0.02 (-0.06 to 0.03)	NS	NS
Timolol	Propranolol	Fatigue/tiredness[60, 61]	242	19.8 [11.6]	1.7 (0.9 to 3.2)	0.08 (-0.01 to 0.17)	NS	NS
Topiramate	Amitriptyline	Adverse events: Any[170, 172]	399	82.7 [87.3]	1.0 (0.9 to 1.0)	-0.04 (-0.11 to 0.02)	NS	NS
Topiramate	Valproate	Hair loss[167, 232]	134	0.0 [4.5]	0.3 (0.0 to 2.2)	-0.04 (-0.10 to 0.02)	NS	NS
Topiramate	**Amitriptyline**	**Weight increase[172, 242]**	**383**	**3.6 [18.7]**	**0.1 (0.0 to 3.7)**	**-0.14 (-0.19 to -0.09)**	**-7 (-11 to -5)**	**-140 (-192 to -88)**
Topiramate	**Amitriptyline**	**Paresthesia[170, 172]**	**399**	**30.4 [4.1]**	**6.7 (3.4 to 13.5)**	**0.26 (0.19 to 0.33)**	**4 (3 to 5)**	**261 (192 to 331)**
Topiramate	**Amitriptyline**	**Weight decrease (loss)[172, 242]**	**383**	**23.8 [4.0]**	**6.3 (2.9 to 13.4)**	**0.24 (0.06 to 0.42)**	**4 (2 to 16)**	**242 (61 to 423)**
Topiramate	Valproate	Weight increase (gain)[167, 232]	134	0.0 [19.4]	0.1 (0.0 to 0.7)	-0.19 (-0.47 to 0.09)	NS	NS
Topiramate	Valproate	Somnolence[167, 232, 243]	210	13.1 [10.7]	0.7 (0.1 to 4.0)	-0.06 (-0.28 to 0.16)	NS	NS
Topiramate	Valproate	Paresthesia[167, 232, 243]	210	24.3 [4.9]	4.3 (0.3 to 56.0)	0.17 (-0.01 to 0.34)	NS	NS
Topiramate	**Valproate**	**Weight decrease (loss)[167, 232]**	**134**	**11.9 [0.0]**	**8.3 (1.1 to 65.1)**	**0.24 (0.06 to 0.42)**	**4 (2 to 16)**	**242 (61 to 423)**
Metoprolol	Aspirin	Diastolic blood pressure[185, 188]	326	0.6 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)	NS	NS
Topiramate	Amitriptyline	Constipation[170, 172]	399	3.0 [13.6]	0.2 (0.0 to 1.5)	-0.25 (-0.65 to 0.16)	NS	NS
Topiramate	Amitriptyline	Hyperesthesia[172]	399	9.4 [10.8]	0.4 (0.0 to 29.7)	-0.23 (-0.82 to 0.37)	NS	NS
Topiramate	Valproate	Weight decrease (loss)[167, 170, 232]	134	11.9 [0.0]	6.3 (2.9 to 13.4)	0.11 (-0.02 to 0.24)	NS	NS

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval; NS= not significant; Number needed to treat and number of attributable events were calculated for statistically significant differences

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Abnormal vision	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	9/178 [5.1]	9/169 [5.3]	0.9 (0.4 to 2.3)	0.00 (-0.05 to 0.04)
Anorexia	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	12/178 [6.7]	8/169 [4.7]	1.4 (0.6 to 3.4)	0.02 (-0.03 to 0.07)
Anorexia	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	1/60 [1.7]	1/60 [1.7]	1.0 (0.1 to 15.6)	0.00 (-0.05 to 0.05)
Constipation	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	6/178 [3.4]	14/169 [8.3]	0.4 (0.2 to 1.0)	-0.05 (-0.10 to 0.00)
Constipation	Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[170] Medium	0/24 [0.0]	13/28 [45.4]	0.0 (0.0 to 0.7)	-0.46 (-0.65 to -0.27)
Coughing	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose	Dodick, 2009[172] Low	9/178 [5.1]	7/169 [4.1]	1.2 (0.5 to 3.2)	0.01 (-0.03 to 0.05)

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Difficulty with concentration/attention	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	12/178 [6.7]	5/169 [3.0]	2.3 (0.8 to 6.3)	0.04 (-0.01 to 0.08)
Distal paresthesia	**Topiramate 100mg BD**	**Levetiracetam 1000mg BD**	de Tommaso, 2007[168] **Medium**	**7/13 [53.8]**	**0/15 [0.0]**	**17.1 (1.1 to 274.0)**	**0.54 (0.26 to 0.81)**
Dizziness	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	15/178 [8.4]	18/169 [10.7]	0.8 (0.4 to 1.5)	-0.02 (-0.08 to 0.04)
Drowsiness	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[168] Medium	3/13 [23.1]	0/15 [0.0]	8.0 (0.5 to 141.8)	0.23 (-0.01 to 0.47)
Dry mouth	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**12/178 [6.7]**	**60/169 [35.5]**	**0.2 (0.1 to 0.3)**	**-0.29 (-0.37 to -0.21)**
Dyspepsia	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose	Dodick, 2009[172] Low	9/178 [5.1]	14/169 [8.3]	0.6 (0.3 to 1.4)	-0.03 (-0.08 to 0.02)

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Fatigue	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	30/178 [16.9]	41/169 [24.3]	0.7 (0.5 to 1.1)	-0.07 (-0.16 to 0.01)
Gastrointestinal intolerance	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Giddiness	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	2/60 [3.3]	2/60 [3.3]	1.0 (0.1 to 6.9)	0.00 (-0.06 to 0.06)
Hair loss	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[167] Medium	0/32 [0.0]	1/32 [3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Headache	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	9/178 [5.1]	0/169 [0.0]	18.0 (1.1 to 307.6)	0.05 (0.02 to 0.08)
Hyperosmia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	Keskinbora, 2008[170] **Medium**	**0/24 [0.0]**	**15/28 [54.6]**	**0.0 (0.0 to 0.6)**	**-0.54 (-0.73 to -0.35)**
Hypoesthesia	**Topiramate 100mg (The starting dosage was 25mg/d**	**Amitriptyline 100mg (The starting dosage was 25mg/d for**	Dodick, 2009[172] **Low**	**19/178 [10.7]**	**6/169 [3.6]**	**3.0 (1.2 to 7.3)**	**0.07 (0.02 to 0.12)**

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	**7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**					
Nausea	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	18/178 [10.1]	12/169 [7.1]	1.4 (0.7 to 2.9)	0.03 (-0.03 to 0.09)
Palpitations	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	0/60 [0.0]	0/60 [0.0]	0.0 (0.0 to 0.0)	0.00 (-0.03 to 0.03)
Paresthesia	Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[170] Medium	4/24 [15.0]	0/28 [0.0]	10.4 (0.6 to 184.6)	0.17 (0.01 to 0.32)
Paresthesia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	Keskinbora, 2008[170] **Medium**	**8/24 [35.0]**	**0/28 [0.0]**	**19.7 (1.2 to 324.8)**	**0.33 (0.14 to 0.52)**
Paresthesia	**Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)**	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	Keskinbora, 2008[170] **Medium**	**10/24 [40.0]**	**0/28 [0.0]**	**24.4 (1.5 to 395.1)**	**0.42 (0.22 to 0.62)**

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Paresthesia	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**53/178 [29.8]**	**8/169 [4.7]**	**6.3 (3.1 to 12.8)**	**0.25 (0.18 to 0.32)**
Paresthesia	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[167] Medium	3/32 [9.4]	0/32 [0.0]	7.0 (0.4 to 130.3)	0.09 (-0.02 to 0.21)
Paresthesia	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Paresthesia	**Topiramate 25mg/day, gradually titrated up to 100mg/day**	**Zonisamide 50mg/day, gradually titrated up to 200mg/day**	**Mohammadiani nejad, 2011[173] Medium**	**9/40 [22.5]**	**0/40 [0.0]**	**19.0 (1.1 to 315.8)**	**0.23 (0.09 to 0.36)**
Paresthesia and weight loss	**Topiramate 50mg (25mg daily increment over 1 week to 50mg)**	**Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)**	Shaygannejad, 2006[167] **Medium**	**8/32 [25.0]**	**0/32 [0.0]**	**17.0 (1.0 to 282.7)**	**0.25 (0.10 to 0.40)**
Pharyngitis	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	8/178 [4.5]	11/169 [6.5]	0.7 (0.3 to 1.7)	-0.02 (-0.07 to 0.03)
Rash	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	0/60 [0.0]	2/60 [3.3]	0.2 (0.0 to 4.1)	-0.03 (-0.09 to 0.02)
Sedation and dizziness in the first days of therapy	Topiramate 100mg BD	Levetiracetam 1000mg BD	de Tommaso, 2007[168] Medium	0/13 [0.0]	5/15 [33.3]	0.1 (0.0 to 1.7)	-0.33 (-0.59 to -0.08)
Sinusitis	Topiramate 100mg (The starting	Amitriptyline 100mg (The starting	Dodick, 2009[172] Low	14/178 [7.9]	18/169 [10.7]	0.7 (0.4 to 1.4)	-0.03 (-0.09 to 0.03)

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Sleepiness and concentration difficulty	Topiramate 25mg BD	Lamotrigine 25mg BD	Gupta, 2007[44] Low	3/60 [5.0]	2/60 [3.3]	1.5 (0.3 to 8.7)	0.02 (-0.05 to 0.09)
Somnolence	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	21/178 [11.8]	30/169 [17.8]	0.7 (0.4 to 1.1)	-0.06 (-0.13 to 0.02)
Somnolence	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[167] Medium	0/32 [0.0]	1/32 [3.1]	0.3 (0.0 to 7.9)	-0.03 (-0.11 to 0.05)
Taste perversion	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	10/178 [5.6]	6/169 [3.6]	1.6 (0.6 to 4.3)	0.02 (-0.02 to 0.06)
Upper respiratory tract infection	Topiramate 100m g(The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	14/178 [7.9]	11/169 [6.5]	1.2 0.6 to 2.6)	0.01 (-0.04 to 0.07)
Viral infection	Topiramate 100mg (The starting	Amitriptyline 100mg (The starting	Dodick, 2009[172] Low	14/178 [7.9]	11/169 [6.5]	1.2 (0.6 to 2.6)	0.01 (-0.04 to 0.07)

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))					
Weight gain	Topiramate 200mg(Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbora, 2008[170] Medium	0/24 [0.0]	8/28 [27.3]	0.1 (0.0 to 1.1)	**-0.29 (-0.46 to -0.11)**
Weight gain	**Topiramate 50mg (25mg daily increment over 1 week to 50mg)**	**Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)**	Shaygannejad, 2006[167] **Risk of bias Medium**	**0/32 [0.0]**	**11/32 [34.4]**	**0.0 (0.0 to 0.7)**	**-0.34 (-0.51 to -0.18)**
Weight increase	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**0/178 [0.0]**	**23/169 [13.6]**	**0.0 (0.0 to 0.3)**	**-0.14 (-0.19 to -0.08)**
Weight loss	Topiramate 50mg (25mg daily increment over 1 week to 50mg)	Sodium valproate 400mg (200mg daily increment over 1 week to 400mg)	Shaygannejad, 2006[167]Medium	6/32 [18.8]	0/32 [0.0]	13.0 (0.8 to 221.5)	**0.19 (0.05 to 0.33)**
Weight loss	**Topiramate 100mg BD**	**Levetiracetam 1000mg BD**	de Tommaso, 2007[168] **Medium**	**8/13 [61.5]**	**0/15 [0.0]**	**19.4 (1.2 to 307.1)**	**0.62 (0.35 to 0.89)**
<1% decrease to <1% increase from baseline	Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or	Dodick, 2009[172] Risk of bias Low	33/178 [18.7]	28/169 [16.5]	1.1 (0.7 to 1.8)	0.02 (-0.06 to 0.10)

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
	BID (or the maximum tolerated dose))	the maximum tolerated dose))					
≥1% loss of body weight during the study	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**115/178 [64.4]**	**32/169 [19.0]**	**3.4 (2.5 to 4.7)**	**0.46 (0.36 to 0.55)**
≥1% to <5% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made u to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**61/178 [34.5]**	**27/169 [15.8]**	**2.1 (1.4 to 3.2)**	**0.18 (0.09 to 0.27)**
≥1% to 5% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**23/178 [12.9]**	**61/169 [36.1]**	**0.4 (0.2 to 0.6)**	**-0.23 (-0.32 to -0.14)**
≥10% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**1/178 [0.6]**	**15/169 [8.9]**	**0.1 (0.0 to 0.5)**	**-0.08 (-0.13 to -0.04)**

Appendix Table D152. Comparative safety of topiramate for migraine prevention in adults (individual randomized controlled clinical trials) (continued)

Adverse Effect	Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
≥10% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**16/178 [8.8]**	**0/169 [0.0]**	**31.3 (1.9 to 518.3)**	**0.09 (0.05 to 0.13)**
≥5% loss of body weight during the study	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**53/178 [29.9]**	**5/169 [3.2]**	**10.1 (4.1 to 24.6)**	**0.27 (0.20 to 0.34)**
≥5% to 10% increase in weight from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**6/178 [3.5]**	**33/169 [19.6]**	**0.2 (0.1 to 0.4)**	**-0.16 (-0.23 to -0.10)**
≥5% to <10% weight decrease from baseline	**Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))**	**Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))**	Dodick, 2009[172] **Low**	**38/178 [21.1]**	**5/169 [3.2]**	**7.2 (2.9 to 17.9)**	**0.18 (0.12 to 0.25)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D153. Adverse effects with migraine preventive drugs compared to each other, significant results from individual randomized controlled clinical trials

Active vs. Control Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Topiramate vs. Amitriptyline	Dry mouth	Low Dodick, 2009[172]	347	6.7 [35.5]	0.2 (0.1 to 0.3)	-0.29 (-0.37 to -0.21)	-3 (-5 to -3)	-288 (-369 to -207)
Topiramate vs. Amitriptyline	Headache	Low Dodick, 2009[172]	347	5.1 [0.0]	18.0 (1.1 to 307.6)	0.05 (0.02 to 0.08)	20 (12 to 60)	51 (17 to 84)
Topiramate vs. Propranolol	Paresthesia	Low Dodick, 2009[172]	288	56.3 [11.8]	4.8 (3.0 to 7.6)	0.44 (0.35 to 0.54)	2 (2 to 3)	444 (348 to 541)
Topiramate vs. Levetiracetam	Paresthesia	Medium de Tommaso, 2007[168]	28	53.8 [0.0]	17.1 (1.1 to 274.0)	0.54 (0.26 to 0.81)	2 (1 to 4)	538 (264 to 813)
Topiramate vs. Propranolol	Concentration/attention: Difficult	Low Diener, 2004[43]	288	15.3 [4.9]	3.1 (1.4 to 7.1)	0.10 (0.04 to 0.17)	10 (6 to 28)	104 (36 to 173)
Topiramate vs. Propranolol	Weight decrease	Low Diener, 2004[43]	288	9.0 [0.0]	27.0 (1.6 to 449.9)	0.09 (0.04 to 0.14)	11 (7 to 24)	90 (42 to 139)
Topiramate vs. Levetiracetam	Sedation and dizziness	Medium de Tommaso, 2007[168]	28	0.0 [33.3]	0.1 (0.0 to 1.7)	-0.33 (-0.59 to -0.08)	-3 (-12 to -2)	-333 (-586 to -81)
Topiramate vs. Levetiracetam	Weight decrease (loss)	Medium de Tommaso, 2007[168]	28	61.5 [0.0]	19.4 (1.2 to 307.1)	0.62 (0.35 to 0.89)	2 (1 to 3)	615 (346 to 885)
Propranolol LA (+ placebo) vs. Atenolol	Physical capacity: reduced	Medium Stensrud, 1980[62]	70	17.1 [2.9]	6.0 (0.8 to 47.3)	0.14 (0.01 to 0.28)	7 (4 to 158)	143 (6 to 279)
Propranolol vs. Clonidine	Insomnia	Medium Kass, 1980[69]	46	21.7 [0.0]	11.0 (0.6 to 188.1)	0.22 (0.04 to 0.39)	5 (3 to 25)	217 (40 to 395)
Propranolol vs. Femoxetine	Mental disorder	Medium Andersson, 1981[177]	49	40.0 [4.2]	9.6 (1.3 to 69.4)	0.36 (0.15 to 0.57)	3 (2 to 7)	358 (150 to 566)
Propranolol vs. Nifedipine	Adverse events (Moderate-Severe):Any	High Albers, 1989[74]	40	65.0 [90.0]	0.7 (0.5 to 1.0)	-0.25 (-0.50 to 0.00)	-4 (-328 to -2)	-250 (-497 to -3)
Propranolol vs. Nifedipine	Dizziness	High Albers, 1989[74]	40	15.0 [65.0]	0.2 (0.1 to 0.7)	-0.50 (-0.76 to -0.24)	-2 (-4 to -1)	-500 (-761 to -239)
Propranolol vs. Nifedipine	Dizziness: Moderate-Severe	High Albers, 1989[74]	40	5.0 [40.0]	0.1 (0.0 to 0.9)	-0.35 (-0.58 to -0.12)	-3 (-9 to -2)	-350 (-585 to -115)
Propranolol vs.	Fatigue: Total	High	40	45.0 [0.0]	19.0	0.45	2 (1 to 4)	450

Appendix Table D153. Adverse effects with migraine preventive drugs compared to each other, significant results from individual randomized controlled clinical trials (continued)

Active vs. Control Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Nifedipine		Albers, 1989[74]			(1.2 to 305.9)	(0.23 to 0.67)		(227 to 673)
Propranolol vs. Nifedipine	Fatigue: Moderate-Severe	High Albers, 1989[74]	40	45.0 [0.0]	19.0 (1.2 to 305.9)	0.45 (0.23 to 0.67)	2 (1 to 4)	450 (227 to 673)
Propranolol vs. Nifedipine	Shakiness: Total	High Albers, 1989[74]	40	0.0 [20.0]	0.1 (0.0 to 1.9)	-0.20 (-0.39 to -0.01)	-5 (-78 to -3)	-200 (-387 to -13)
Propranolol vs. Nifedipine	Concentration decreased	High 2654067	40	0.0 [20.0]	0.1 (0.0 to 1.9)	-0.20 (-0.39 to -0.01)	-5 (-78 to -3)	-200 (-387 to -13)
Propranolol vs. Nifedipine	Tachycardia	High Albers, 1989[74]	40	0.0 [30.0]	0.1 (0.0 to 1.3)	-0.30 (-0.51 to -0.09)	-3 (-11 to -2)	-300 (-508 to -92)
Propranolol vs. Nifedipine	Nausea	High Albers, 1989[74]	40	0.0 [30.0]	0.1 (0.0 to 1.3)	-0.30 (-0.51 to -0.09)	-3 (-11 to -2)	-300 (-508 to -92)
Propranolol vs. Nifedipine	Warm, swollen red legs: Moderate-Severe	High Albers, 1989[74]	40	0.0 [30.0]	0.1 (0.0 to 1.3)	-0.30 (-0.51 to -0.09)	-3 (-11 to -2)	-300 (-508 to -92)
Propranolol vs. Nifedipine	Warm, swollen red legs: Total	High Albers, 1989[74]	40	0.0 [45.0]	0.1 (0.0 to 0.8)	-0.45 (-0.67 to -0.23)	-2 (-4 to -1)	-450 (-673 to -227)
Propranolol vs. Nifedipine	Facial flushing	High Albers, 1989[74]	40	0.0 [30.0]	0.1 (0.0 to 1.3)	-0.30 (-0.51 to -0.09)	-3 (-11 to -2)	-300 (-508 to -92)
Propranolol vs. Nifedipine	Facial flushing: Moderate-Severe	High Albers, 1989[74]	40	0.0 [20.0]	0.1 (0.0 to 1.9)	-0.2 0(-0.39 to -0.01)	-5 (-78 to -3)	-200 (-387 to -13)
Metoprolol vs. Nebivolol	Adverse events: Moderate	Medium Schellenberg, 2008[189]	30	85.7 [37.5]	2.3 (1.2 to 4.5)	0.48 (0.18 to 0.78)	2 (1 to 5)	482 (182 to 782)
Metoprolol vs. Nebivolol	Fatigue	Medium Schellenberg, 2008[189]	30	78.6 [43.8]	1.8 (1.0 to 3.3)	0.35 (0.02 to 0.67)	3 (1 to 42)	348 (24 to 673)
Metoprolol vs. Nebivolol	Bradycardia	Medium Schellenberg, 2008[189]	30	35.7 [6.3]	5.7 (0.8 to 43.2)	0.2 9(0.02 to 0.57)	3 (2 to 59)	295 (17 to 572)
Metoprolol vs. Aspirin	Adverse events	Low Diener, 2001[188]	270	73.3 [37.8]	1.9 (1.5 to 2.5)	0.36 (0.24 to 0.47)	3 (2 to 4)	356 (245 to 466)
Metoprolol vs. Aspirin	Autonomic nervous system disorders	Low Diener, 2001[188]	270	8.1 [0.0]	23.0 (1.4 to 386.4)	0.08 (0.03 to 0.13)	12 (8 to 30)	81 (34 to 129)
Metoprolol vs. Aspirin	Body as a whole general disorders	Low Diener, 2001[188]	270	8.1 [2.2]	3.7 (1.0 to 12.9)	0.06 (0.01 to 0.11)	17 (9 to 146)	59 (7 to 112)
Metoprolol vs. Aspirin	Psychiatric disorders	Low Diener, 2001[188]	270	11.9 [1.5]	8.0 (1.9 to 34.1)	0.10 (0.05 to 0.16)	10 (6 to 22)	104 (45 to 162)

Appendix Table D153. Adverse effects with migraine preventive drugs compared to each other, significant results from individual randomized controlled clinical trials (continued)

Active vs. Control Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Metoprolol vs. Aspirin	Vascular disorders	Low Diener, 2001[188]	270	3.7 [0.0]	11.0 (0.6 to 197.0)	0.04 (0.00 to 0.07)	27 (14 to 416)	37 (2 to 72)
Metoprolol vs. Aspirin	Skin and appendices disorders	Low Diener, 2001[188]	270	6.7 [1.5]	4.5 (1.0 to 20.4)	0.05 (0.01 to 0.10)	19 (10 to 196)	52 (5 to 99)
Clomipramine vs. Metoprolol	Insomnia	Medium Langohr, 1985[184]	126	23.8 [3.2]	7.5 (1.8 to 31.4)	0.21 (0.09 to 0.32)	5 (3 to 11)	206 (93 to 320)
Clomipramine vs. Metoprolol	Sweating	Medium Langohr, 1985[184]	126	14.3 [1.6]	9.0 (1.2 to 69.0)	0.13 (0.04 to 0.22)	8 (5 to 28)	127 (35 to 219)
Clomipramine vs. Metoprolol	Constipation	Medium Langohr, 1985[184]	126	9.5 [1.6]	6.0 (0.7 to 48.4)	0.08 (0.00 to 0.16)	13 (6 to 1716)	79 (1 to 158)
Femoxetine vs. propranolol	Dizziness	Medium Kangasniemi, 1983[77]	48	41.7 [12.5]	3.3 (1.0 to 10.6)	0.29 (0.05 to 0.53)	3 (2 to 18)	292 (54 to 529)
Femoxetine vs. propranolol	Tiredness	Medium Kangasniemi, 1983[77]	48	37.5 [4.2]	9.0 (1.2 to 65.6)	0.33 (0.12 to 0.54)	3 (2 to 8)	333 (124 to 543)
Fluoxetine vs. Amitriptyline	Adverse events, no detailed information	Medium Oguzhanoglu, 1999[107]	47	40.0 [77.3]	0.5 (0.3 to 0.9)	-0.37 (-0.63 to -0.11)	-3 (-9 to -2)	-373 (-633 to -113)
Nortriptyline vs. Propranolol	Sleepiness (Somnolence)	Medium Domingues, 2009[75]	49	25.0 [4.0]	6.3 (0.8 to 48.1)	0.21 (0.02 to 0.40)	5 (3 to 49)	210 (20 to 400)
Venlafaxine vs. Amitriptyline	Dry mouth	Medium Bulut, 2004[109]	104	5.8 [69.2]	0.1 (0.0 to 0.3)	-0.63 (-0.78 to -0.49)	-2 (-2 to -1)	-635 (-775 to -494)
Venlafaxine vs. Amitriptyline	Memory loss	Medium Bulut, 2004[109]	104	1.9 [17.3]	0.1 (0.0 to 0.8)	-0.15 (-0.26 to -0.04)	-6 (-22 to -4)	-154 (-263 to -44)
Venlafaxine vs. Amitriptyline	Sedation	Medium Bulut, 2004[109]	104	11.5 [34.6]	0. 3(0.1 to 0.8)	-0.23 (-0.39 to -0.08)	-4 (-13 to -3)	-231 (-387 to -75)
Venlafaxine vs. Amitriptyline	Concentration difficult	Medium Bulut, 2004[109]	104	5.8 [53.8]	0.1 (0.0 to 0.3)	-0.48 (-0.63 to -0.33)	-2 (-3 to -2)	-481 (-630 to -331)
Venlafaxine vs. Amitriptyline	Orthostatic hypotension	Medium Bulut, 2004[109]	104	1.9 [30.8]	0.1 (0.0 to 0.5)	-0.29 (-0.42 to -0.16)	-3 (-6 to -2)	-288 (-419 to -158)
Venlafaxine vs. Amitriptyline	Weight increase (gain)	Medium Bulut, 2004[109]	104	1.9 [15.4]	0.1 (0.0 to 1.0)	-0.13 (-0.24 to -0.03)	-7 (-34 to -4)	-135 (-240 to -30)
Venlafaxine vs. Amitriptyline	Weight decrease (Loss of weight)	Medium Bulut, 2004[109]	104	9.6 [0.0]	11.0 (0.6 to 194.0)	0.10 (0.01 to 0.18)	10 (5 to 100)	96 (10 to 182)
Venlafaxine vs. Amitriptyline	Blurred vision	Medium Bulut, 2004[109]	104	0.0 [13.5]	0.1 (0.0 to 1.1)	-0.13 (-0.23 to -0.04)	-7 (-27 to -4)	-135 (-232 to -37)

Appendix Table D153. Adverse effects with migraine preventive drugs compared to each other, significant results from individual randomized controlled clinical trials (continued)

Active vs. Control Drug	Adverse Effect	Risk of Bias Reference	Sample	% with Active [Control] Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)	Number Needed to Treat to Harm (95% CI)	Attributable Events per 1000 Treated (95% CI)
Amitriptyline vs. Propranolol	Blurred vision	Medium Rafieian-Kopaei, 2005[64]	105	66.7 [31.3]	2.1 (1.2 to 3.8)	0.35 (0.12 to 0.59)	3 (2 to 8)	354 (121 to 587)
Lisuride vs. Methysergide	Cold feeling	Medium Hermann, 1977[153]	253	7.7 [0.0]	19.9 (1.2 to 335.6)	0.08 (0.03 to 0.12)	13 (8 to 34)	77 (29 to 125)
Lisuride vs. Methysergide	Muscle weakness	Medium Hermann, 1977[153]	253	7.7 [0.0]	19.9 (1.2 to 335.6)	0.08 (0.03 to 0.12)	13 (8 to 34)	77 (29 to 125)

Appendix Table D154. Risk of any adverse effects with topiramate vs. amitriptyline for migraine prevention in adults

Topiramate, Daily Dose	Control Drug, Daily Dose	Reference Risk of Bias	Events/ Randomized [Rate, %] with Topiramate	Events/ Randomized [Rate, %] with Control Drug	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	**Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)**	**Keskinbor, 2008[170] Medium**	**9/23 [39.1]**	**22/28 [78.6]**	**0.5 (0.3 to 0.9)**	**-0.39 (-0.65 to -0.14)**
Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Amitriptyline 150mg (Initiated at a dose of 10mg/day and increased in weekly increments of 10-25mg/day to a maximum dose of 150mg/day)	Keskinbor, 2008[170] Medium	15/24 [62.5]	22/28 [78.6]	0.8 (0.6 to 1.1)	-0.16 (-0.41 to 0.09)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	121/178 [68.0]	128/169 [75.7]	0.9 (0.8 to 1.0)	-0.08 (-0.17 to 0.02)
Topiramate 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25mg/d were made up to 50mg BID (or the maximum tolerated dose))	Amitriptyline 100mg (The starting dosage was 25mg/d for 7 days. Weekly dose titrations of 25m/d were made up to 50mg BID (or the maximum tolerated dose))	Dodick, 2009[172] Low	152/178 [85.4]	150/169 [88.8]	1.0 (0.9 to 1.0)	-0.03 (-0.10 to 0.04)
Topiramate 200mg (Initiated at a dose of 25mg/day and increased in weekly increments of 25mg/day to a maximum dose of 200mg)	Topiramate + Amitriptyline Initial doses of topiramate 25mg/day and amitriptyline 10mg/day and this was followed by weekly increases of 25mg/day topiramate and 10mg/day amitriptyline	Keskinbora, 2008[170] Medium	15/24 [62.5]	9/23 [39.1]	1.6 (0.9 to 2.9)	0.23 (-0.04 to 0.51)

Bold = significant difference at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D155. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials)

Active Treatment	Control Treatment	Reference Risk of Bias	Events/ Randomized with Active Treatment	Events/ Randomized with Control Treatment	Rate, % with Active [Control] Treatment	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Propranolol + Amitriptyline Propranolol: 160 mg; Amitriptyline: 75 mg	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[105] Risk of bias High	2/41	4/45	5 [9]	0.5 (0.1 to 2.8)	-0.04 (-0.15 to 0.07)
Propranolol + Amitriptyline Propranolol: 160 mg; Amitriptyline: 75 mg	**Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.**	**Mathew, 1981[105] Risk of bias High**	**2/47**	**9/49**	**4 [18]**	**0.2 (0.1 to 1.0)**	**-0.14 (-0.26 to -0.02)**
Propranolol + Amitriptyline + Biofeedback Propranolol: 160 mg; Amitriptyline: 75 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[105] Risk of bias High	4/46	9/49	9 [18]	0.5 (0.2 to 1.4)	-0.10 (-0.23 to 0.04)
Propranolol + Amitriptyline + Biofeedback Propranolol: 160 mg; Amitriptyline: 75 mg;	Abortive treatment with ergotamine and analgesics (control)	Mathew, 1981[105] Risk of bias High	3/38	4/45	8 [9]	0.9 (0.2 to 3.7)	-0.01 (-0.13 to 0.11)

Appendix Table D155. Treatment discontinuation due to adverse effects with propranolol for migraine prevention in adults (results from randomized controlled clinical trials) (continued)

Active Treatment	Control Treatment	Reference Risk of Bias	Events/ Randomized with Active Treatment	Events/ Randomized with Control Treatment	Rate, % with Active [Control] Treatment	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Total ergotamine intake was restricted to 6 mg a week.						
Propranolol + Biofeedback Propranolol: 160 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[105] Risk of bias High	2/39	4/45	5 [9]	0.6 (0.1 to 3.0)	-0.04 (-0.15 to 0.07)
Propranolol + Biofeedback Propranolol: 160 mg; Biofeedback: 10 x 1hr session of combined electromyographic and temperature regulation training; instructed to practice biofeedback at least once a day for minimum of 30 minutes	Abortive treatment with ergotamine and analgesics (control) Total ergotamine intake was restricted to 6 mg a week.	Mathew, 1981[105] Risk of bias High	3/43	9/49	7 [18]	0.4 (0.1 to 1.3)	-0.11 (-0.25 to 0.02)

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D156. 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) vs. beta-blockers alone for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial[193]

Definition of the Outcome	Active Treatment	Control Treatment	Events Randomized with Active Treatment	Events/ Randomized with Control Treatment	Rate in Active Group,% [Control Group]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Clinically improved (≥50% reduction in migraines) at month 10	Behavioral migraine management + Placebo	Propranolol/nadolol	19/55	18/53	34.5 [34.0]	1.0 (0.6 to 1.7)	0.01 (-0.17 to 0.18)
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + Propranolol/nadolol**	**Propranolol/nadolol**	**53/69**	**18/53**	**76.8 [34.0]**	**2.3 (1.5 to 3.4)**	**0.43 (0.27 to 0.59)**
Clinically improved (≥50% reduction in migraines) at month 10	**Behavioral migraine management + placebo**	**Behavioral migraine management + Propranolol/nadolol**	**19/55**	**53/69**	**34.5 [76.8]**	**0.4 (0.3 to 0.7)**	**-0.42 (-0.58 to -0.26)**
Dropped out	Behavioral migraine management + Placebo	Propranolol/nadolol	22/55	27/53	40.0 [50.9]	0.8 (0.5 to 1.2)	-0.11 (-0.30 to 0.08)
Dropped out	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	24/69	27/53	34.8 [50.9]	0.7 (0.4 to 1.0)	-0.16 (-0.34 to 0.01)
Dropped out	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	22/55	24/69	40.0 [34.8]	1.2 (0.7 to 1.8)	0.05 (-0.12 to 0.22)
Dropped due to side - effects	Behavioral migraine management + Placebo	Propranolol/nadolol	5/55	7/53	9.1 [13.2]	0.7 (0.2 to 2.0)	-0.04 (-0.16 to 0.08)
Dropped due to side - effects	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	6/69	7/53	8.7 [13.2]	0.7 (0.2 to 1.8)	-0.05 (-0.16 to 0.07)
Dropped out due to side effects	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	5/55	6/69	9.1 [8.7]	1.0 (0.3 to 3.2)	0.00 (-0.10 to 0.10)

Appendix Table 156. 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) vs. beta-blockers alone for migraine prevention in adults, results from individual low risk of bias randomized controlled clinical trial (continued)

Definition of the Outcome	Active Treatment	Control Treatment	Events Randomized with Active Treatment	Events/ Randomized with Control Treatment	Rate in Active Group,% [Control Group]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Dropped due to lack of efficacy	Behavioral migraine management + Propranolol/nadolol	Propranolol/nadolol	1/69	5/53	1.4 [9.4]	0.2 (0.0 to 1.3)	-0.08 (-0.16 to 0.00)
Dropped due to lack of efficacy	Behavioral migraine management + Placebo	Propranolol/nadolol	4/55	5/53	7.3 [9.4]	0.8 (0.2 to 2.7)	-0.02 (-0.13 to 0.08)
Dropped out due to lack of efficacy	Behavioral migraine management + placebo	Behavioral migraine management + Propranolol/nadolol	4/55	1/69	7.3 [1.4]	5.0 (0.6 to 43.6)	0.06 (-0.02 to 0.13)

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D157. Headache specific locus of control at month 16 with 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) vs. beta-blockers alone for migraine prevention in adults, results from individual medium risk of bias randomized controlled clinical trial[207]

Outcome	Active	Control	Randomized for Active [Control] Treatment	Mean [Standard Deviation] with Active Treatment	Mean [Standard Deviation] with Control Treatment	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Mean Change HSLC (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**21.4 [6.9]**	**26.4 [9.0]**	**-5.0 (-8.0 to -2.0)**	**-0.6 (-1.0 to -0.2)**
Mean Change HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**21.1 [8.4]**	**26.4 [9.0]**	**-5.3 (-8.4 to -2.2)**	**-0.6 (-1.0 to -0.2)**
Mean Change Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	21.4 [6.9]	21.1 [8.4]	0.3 (-2.4 to 3.0)	0.0 (-0.3 to 0.4)
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	Placebo + Behavioral Migraine Management	Propranolol HCL/nadolol	55 [53]	32.9 [5.8]	35.1 [6.7]	-2.2 (-4.6 to 0.2)	-0.4 (-0.7 to 0.0)
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**31.6 [6.9]**	**35.1 [6.7]**	**-3.5 (-5.9 to -1.1)**	**-0.5 (-0.9 to -0.1)**
Mean Medical Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	32.9 [5.8]	31.6 [6.9]	1.3 (-0.9 to 3.5)	0.2 (-0.2 to 0.6)
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**63.4 [6.8]**	**57.7 [8.9]**	**5.7 (2.7 to 8.7)**	**0.7 (0.3 to 1.1)**

Appendix Table 157. Headache Specific Locus of Control at month 16 with 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) vs. beta-blockers alone for migraine prevention in adults, results from individual medium risk of bias randomized controlled clinical trial (continued)

Outcome	Active	Control	Randomized for Active [Control] Treatment	Mean [Standard Deviation] with Active Treatment	Mean [Standard Deviation] with Control Treatment	Mean Difference (95% CI)	Cohen Standardized Mean Difference (95% CI)
Mean Internal HSLC (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**63.9 [7.7]**	**57.7 [8.9]**	**6.2 (3.2 to 9.2)**	**0.8 (0.4 to 1.1)**
Mean Internal Professionals HSLC (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	63.4 [6.8]	63.9 [7.7]	-0.5 (-3.1 to 2.1)	-0.1 (-0.4 to 0.3)
Mean HSE (Headache Specific Locus of Control) at month 16	**Placebo + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**55 [53]**	**143.4 [20.0]**	**127.5 [21.9]**	**15.9 (8.0 to 23.8)**	**0.8 (0.4 to 1.1)**
Mean HSE (Headache Specific Locus of Control) at month 16	**Propranolol HCL/nadolol + Behavioral Migraine Management**	**Propranolol HCL/nadolol**	**69 [53]**	**144.8 [23.6]**	**127.5 [21.9]**	**17.3 (9.2 to 25.4)**	**0.8 (0.4 to 1.1)**
Mean HSE (Headache Specific Locus of Control) at month 16	Behavioral Migraine Management + Placebo	Propranolol HCL/nadolol + Behavioral Migraine Management	55 [69]	143.4 [20.0]	144.8 [23.6]	-1.4 (-9.1 to 6.3)	-0.1 (-0.4 to 0.3)

Bold = significant at 95% confidence limit when 95% CI of mean difference estimates do not include 0
CI = confidence interval

Appendix Table D158. Strength of evidence of 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	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Withdrew because of side effects and/or lack of efficacy	Louis, 1985[183]	Metoprolol	Clonidine	Medium	Yes	Not applicable	No	Low
Discontinued due to side-effects	Worz, 1991[186]	Metoprolol	Bisoprolol	Medium	Yes	Not applicable	No	Low
Patient withdrawal due to events	Schellenberg, 2008[189]	Metoprolol	Nebivolol	Medium	Yes	Not applicable	No	Low
Drowsiness leading to withdrawal	Grotemeyer, 1990[185]	Metoprolol	Aspirin	Medium	Yes	Not applicable	No	Low
Gastrointestinal side-effects leading to withdrawal	Grotemeyer, 1990[185]	Metoprolol	Aspirin	Medium	Yes	Not applicable	No	Low
Discontinued treatment because of severe adverse reactions	Langohr, 1985[184]	Clomipramine	Metoprolol	Medium	Yes	Not applicable	No	Low

Appendix Table D159. Comparative safety of beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Insomnia	**Langohr, 1985[184] Medium**	**Clomipramine 100mg/day**	**Metoprolol 100mg/day**	**15/63 [23.8]**	**2/63 [3.2]**	**7.5 (1.8 to 31.4)**	**0.21 (0.09 to 0.32)**
Sweating	**Langohr, 1985[184] Medium**	**Clomipramine 100mg/day**	**Metoprolol 100mg/day**	**9/63 [14.3]**	**1/63 [1.6]**	**9.0 (1.2 to 69.0)**	**0.13 (0.04 to 0.22)**
Tiredness	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	7/63 [11.1]	9/63 [14.3]	0.8 (0.3 to 2.0)	-0.03 (-0.15 to 0.08)
Constipation	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	6/63 [9.5]	1/63 [1.6]	6.0 (0.7 to 48.4)	0.08 (0.00 to 0.16)
Nausea	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	5/63 [7.9]	2/63 [3.2]	2.5 (0.5 to 12.4)	0.05 (-0.03 to 0.13)
Dizziness	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	4/63 [6.3]	1/63 [1.6]	4.0 (0.5 to 34.8)	0.05 (-0.02 to 0.12)
Loss of appetite	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	3/63 [4.8]	1/63 [1.6]	3.0 (0.3 to 28.1)	0.03 (-0.03 to 0.09)
Restlessness	Langohr, 1985[184] Medium	Clomipramine 100mg/day	Metoprolol 100mg/day	2/63 [3.2]	2/63 [3.2]	1.0 (0.1 to 6.9)	0.00 (-0.06 to 0.06)
Adverse events	Worz, 1991[186] Medium	Metoprolol 50 to 100mg twice daily	Bisoprolol 5 to 10mg once daily	18/78 [23.1]	23/78 [29.5]	0.8 (0.5 to 1.3)	-0.06 (-0.20 to 0.07)
Dizziness	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	4/125 [3.2]	8/125 [6.4]	0.5 (0.2 to 1.6)	-0.03 (-0.08 to 0.02)
Tiredness/fatigue	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	7/125 [5.6]	3/125 [2.4]	2.3 (0.6 to 8.8)	0.03 (-0.02 to 0.08)
Sleep disturbances	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	6/125 [4.8]	2/125 [1.6]	3.0 (0.6 to 14.6)	0.03 (-0.01 to 0.08)
Cardiovascular, hypotensive reactions	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	1/125 [0.8]	6/125 [4.8]	0.2 (0.0 to 1.4)	-0.04 (-0.08 to 0.00)

Appendix Table 159. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Gastrointestinal disturbances	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	2/125 [1.6]	5/125 [4.0]	0.4 (0.1 to 2.0)	-0.02 (-0.06 to 0.02)
Adverse effects	Worz, 1992[187] Medium	Metoprolol 50mg BID (max. 200mg daily after 4 weeks)	Bisoprolol 5mg/day (max. 10mg daily after 4 weeks)	19/125 [15.2]	23/125 [18.4]	0.8 (0.5 to 1.4)	-0.03 (-0.12 to 0.06)
Patients with treatment-related events	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	13/14 [92.9]	11/16 [68.8]	1.4 (0.9 to 1.9)	0.24 (-0.02 to 0.51)
Patients reporting mild events	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	1/14 [7.1]	4/16 [25.0]	0.3 (0.0 to 2.3)	-0.18 (-0.43 to 0.07)
Patients reporting moderate events	**Schellenberg, 2008[189] Medium**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**12/14 [85.7]**	**6/16 [37.5]**	**2.3 (1.2 to 4.5)**	**0.48 (0.18 to 0.78)**
Patients reporting severe events	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	6/14 [42.9]	2/16 [12.5]	3.4 (0.8 to 14.3)	0.30 (0.00 to 0.61)
Fatigue	**Schellenberg, 2008[189] Medium**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**11/14 [78.6]**	**7/16 [43.8]**	**1.8 (1.0 to 3.3)**	**0.35 (0.02 to 0.67)**
Bradycardia	**Schellenberg, 2008[189] Medium**	**Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg**	**Nebivolol 5mg daily**	**5/14 [35.7]**	**1/16 [6.3]**	**5.7 (0.8 to 43.2)**	**0.29 (0.02 to 0.57)**

Appendix Table 159. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Hypotension	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	1/16 [6.3]	2.3 (0.2 to 22.6)	0.08 (-0.14 to 0.30)
Supraventricular extrasystoles	Schellenberg, 2008[189] Medium	Metoprolol Week 1: 47.5mg, week 2: 95mg, week 3 - 16:142.5mg	Nebivolol 5mg daily	2/14 [14.3]	0/16 [0.0]	5.7 (0.3 to 108.9)	0.14 (-0.06 to 0.35)
At least one adverse effect	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	53/135 [39.3]	42/135 [31.1]	1.3 (0.9 to 1.8)	0.08 (-0.03 to 0.19)
Skin disorders	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 300mg/day**	**9/135 [6.7]**	**2/135 [1.5]**	**4.5 (1.0 to 20.4)**	**0.05 (0.01 to 0.10)**
Muscular-skeletal system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	2/135 [1.5]	0.5 (0.0 to 5.4)	-0.01 (-0.03 to 0.02)
Central & peripheral nervous system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	4/135 [3.0]	3/135 [2.2]	1.3 (0.3 to 5.8)	0.01 (-0.03 to 0.05)
Autonomic nervous system disorders	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week**	**Aspirin 300mg/day**	**11/135 [8.1]**	**0/135 [0.0]**	**23.0 (1.4 to 386.4)**	**0.08 (0.03 to 0.13)**

Appendix Table 159. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
		and 200mg/day thereafter)					
Vision disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Hearing and vestibular disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Psychiatric disorders	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 300mg/day**	**16/135 [11.9]**	**2/135 [1.5]**	**8.0 (1.9 to 34.1)**	**0.10 (0.05 to 0.16)**
Gastrointestinal system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	25/135 [18.5]	30/135 [22.2]	0.8 (0.5 to 1.3)	-0.04 (-0.13 to 0.06)
Liver and biliary system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	1/135 [0.7]	1.0 (0.1 to 15.8)	0.00 (-0.02 to 0.02)
Endocrine disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	0/135 [0.0]	1/135 [0.7]	0.3 (0.0 to 8.1)	-0.01 (-0.03 to 0.01)

Appendix Table 159. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Cardiovascular disorders, general	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	0/135 [0.0]	3.0 (0.1 to 73.0)	0.01 (-0.01 to 0.03)
Vascular (extracardiac) disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	5/135 [3.7]	0/135 [0.0]	11.0 (0.6 to 197.0)	0.04 (0.00 to 0.07)
Respiratory system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	6/135 [4.4]	1/135 [0.7]	6.0 (0.7 to 49.2)	0.04 (0.00 to 0.07)
White blood cell disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	2/135 [1.5]	0/135 [0.0]	5.0 (0.2 to 103.2)	0.01 (-0.01 to 0.04)
Urinary system disorders	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	2/135 [1.5]	4/135 [3.0]	0.5 (0.1 to 2.7)	-0.01 (-0.05 to 0.02)
Reproductive disorders, female	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	2/135 [1.5]	1/135 [0.7]	2.0 (0.2 to 21.8)	0.01 (-0.02 to 0.03)
Body as a whole general disorders	**Diener, 2001[188] Low**	**Metoprolol 200mg/day**	**Aspirin 300mg/day**	**11/135 [8.1]**	**3/135 [2.2]**	**3.7 (1.0 to 12.9)**	**0.06 (0.01 to 0.11)**

Appendix Table 159. Comparative safety beta-blockers for migraine prevention in adults, adverse effects in randomized controlled clinical trials (continued)

Adverse Effect	Reference Risk of Bias	Active Drug Dose	Control Drug Dose	Events/ Randomized [Rate of Outcome in Active Group, %]	Events/ Randomized [Rate of Outcome in Control Group, %]	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
		(100mg/day in the first week and 200mg/day thereafter)					
Non-medical	Diener, 2001[188] Low	Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)	Aspirin 300mg/day	1/135 [0.7]	1/135 [0.7]	1.0 (0.1 to 15.8)	0.00 (-0.02 to 0.02)
Total adverse effects	**Diener, 2001[188] Low**	**Metoprolol 200mg/day (100mg/day in the first week and 200mg/day thereafter)**	**Aspirin 300mg/day**	**99/135 [73.3]**	**51/135 [37.8]**	**1.9 (1.5 to 2.5)**	**0.36 (0.24 to 0.47)**

Bold = significant differences at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D160. Strength of evidence about treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual medium risk of bias randomized controlled clinical trial[204]

Definition of the Outcome	Active Treatment	Control Treatment	Risk of Bias	Directness	Consistency	Precision	Strength of Evidence
Withdrawn due to side-effects	Spinal Manipulation	Amitriptyline	Medium	Yes	NA	No	Low
Withdrawn due to side-effects	Spinal Manipulation + Amitriptyline	Amitriptyline	Medium	Yes	NA	No	Low
Withdrawn due to side-effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline	Medium	Yes	NA	No	Low

Appendix Table D161. Treatment adherence and discontinuation due to adverse effects with antidepressant amitriptyline and spinal manipulation for migraine prevention in adults, individual medium risk of bias randomized controlled clinical trial[204]

Outcome	Active Treatment	Control Treatment	Events/Randomized Rate, % with Active Treatment	Events/Randomized Rate, % with Control Treatment	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Withdrawn due to side-effects	**Spinal Manipulation The spinal manipulation administered was a type described as high-velocity, low-amplitude, and short-lever arm.**	**Amitriptyline 100mg/day**	**0/7 0.05**	**7/77 10.05**	**0.1 (0.0 to 1.0)**	**-0.10 (-0.17 to -0.03)**
Withdrawn due to side-effects	Spinal Manipulation + Amitriptyline 100mg/day	Amitriptyline 100mg/day	4/7 5.65	7/71 10.05	0.6 (0.2 to 1.8)	-0.04 (-0.13 to 0.04)
Withdrawn due to side-effects	Spinal Manipulation	Spinal Manipulation + Amitriptyline 100mg/day	0/4 0.05	4/77 5.65	0.1 (0.0 to 1.9)	-0.06 (-0.11 to 0.00)
Withdrawn	Spinal Manipulation +Amitriptyline 100mg/day	Amitriptyline 100mg/day	17/15 23.95	15/71 21.45	1.1 (0.6 to 2.1)	0.03 (-0.11 to 0.16)
Withdrawn	Spinal Manipulation	Amitriptyline 100mg/day	19/15 24.75	15/77 21.45	1.2 (0.6 to 2.1)	0.03 (-0.10 to 0.17)
Withdrawn	Spinal Manipulation	Amitriptyline + Spinal Manipulation	19/17 24.75	17/77 23.95	1.0 (0.6 to 1.8)	0.01 (-0.13 to 0.15)

Bold = significant at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D162. Indirect adjusted analysis of the comparative effects on the treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (results with approved drugs and statistically significant results when off label drugs were compared with each other) (strength of evidence is low due to risk of bias and imprecision)

Active Drug, Reference	Control Drug, Reference	Odds Ratio with Active Drug vs. Placebo (95% CI)	Odds Ratio with Control Drug vs. Placebo (95% CI)	Odds Ratio of Active vs. Control Drug (95% CI)	Risk of Bias in Body of Evidence
Divalproex[45, 46]	Timolol[79]	1.3 (0.5 to 3.1)	5.2 (0.2 to 111.7)	0.2 (0.0 to 5.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Timolol[79]	2.0 (1.4 to 2.8)	5.2 (0.2 to 111.7)	0.4 (0.0 to 8.2)	Medium
Propranolol[50, 53]	Timolol[79]	2.4 (0.7 to 8.5)	5.2 (0.2 to 111.7)	0.5 (0.0 to 12.6)	Medium
Divalproex[45, 46]	Propranolol[50, 53]	1.3 (0.5 to 3.1)	2.4 (0.7 to 8.5)	0.5 (0.1 to 2.5)	Medium
Divalproex[45, 46]	Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	1.3 (0.5 to 3.1)	2.0 (1.4 to 2.8)	0.6 (0.2 to 1.7)	Medium
Propranolol[50, 53]	Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	2.4 (0.7 to 8.5)	2.0 (1.4 to 2.8)	1.2 (0.3 to 4.6)	Medium
Divalproex[45, 46]	Pindolol[89]	1.3 (0.5 to 3.1)	7.8 (0.4 to 158.9)	0.2 (0.0 to 3.7)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Pindolol[89]	2.0 (1.4 to 2.8)	7.8 (0.4 to 158.9)	0.3 (0.0 to 5.2)	Medium
Propranolol[50, 53]	Pindolol[89]	2.4 (0.7 to 8.5)	7.8 (0.4 to 158.9)	0.3 (0.0 to 8.0)	Medium
Divalproex[45, 46]	Carbamazepine[86]	1.3 (0.5 to 3.1)	3.1 (0.1 to 77.1)	0.4 (0.0 to 11.7)	Medium
Timolol[79]	Pindolol[89]	5.2 (0.2 to 111.7)	7.8 (0.4 to 158.9)	0.7 (0.0 to 49.0)	Medium
Divalproex[45, 46]	Nifedipine[129]	1.3 (0.5 to 3.1)	6.1 (0.6 to 56.4)	0.2 (0.0 to 2.3)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Carbamazepine[86]	2.0 (1.4 to 2.8)	3.1 (0.1 to 77.1)	0.6 (0.0 to 16.5)	Medium
Propranolol[50, 53]	Carbamazepine[86]	2.4 (0.7 to 8.5)	3.1 (0.1 to 77.1)	0.8 (0.0 to 25.0)	Medium
Timolol[79]	Acetazolamide[80]	5.2 (0.2 to 111.7)	6.6 (1.3 to 34.5)	0.8 (0.0 to 25.6)	Medium
Timolol[79]	Nifedipine[129]	5.2 (0.2 to 111.7)	6.1 (0.6 to 56.4)	0.9 (0.0 to 38.2)	Medium
Timolol[79]	Carbamazepine[86]	5.2 (0.2 to 111.7)	3.1 (0.1 to 77.1)	1.7 (0.0 to 145.7)	Medium
Divalproex[45, 46]	Acetazolamide[80]	1.3 (0.5 to 3.1)	6.6 (1.3 to 34.5)	0.2 (0.0 to 1.2)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Nifedipine[129]	2.0 (1.4 to 2.8)	6.1 (0.6 to 56.4)	0.3 (0.0 to 3.1)	Medium
Propranolol[50, 53]	Nifedipine[129]	2.4 (0.7 to 8.5)	6.1 (0.6 to 56.4)	0.4 (0.0 to 5.2)	Medium
Divalproex[45, 46]	Mg[194, 195]	1.3 (0.5 to 3.1)	4.1 (0.7 to 25.7)	0.3 (0.0 to 2.3)	Medium
Propranolol[50, 53]	Acetazolamide[80]	2.4 (0.7 to 8.5)	6.6 (1.3 to 34.5)	0.4 (0.0 to 2.9)	Medium
Divalproex[45, 46]	Tonabersat[121]	1.3 (0.5 to 3.1)	2.2 (0.2 to 25.4)	0.6 (0.0 to 7.4)	Medium
Timolol[79]	Mg[194, 195]	5.2 (0.2 to 111.7)	4.1 (0.7 to 25.7)	1.3 (0.0 to 45.0)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Acetazolamide[80]	2.0 (1.4 to 2.8)	6.6 (1.3 to 34.5)	0.3 (0.1 to 1.6)	Medium
Divalproex[45, 46]	Clonidine[146, 148]	1.3 (0.5 to 3.1)	2.9 (0.4 to 19.3)	0.4 (0.1 to 3.5)	Medium
Divalproex[45, 46]	Lamotrigine[44, 87]	1.3 (0.5 to 3.1)	2.9 (0.4 to 21.6)	0.4 (0.1 to 4.0)	Medium
Divalproex[45, 46]	Tolfenamic Acid[202]	1.3 (0.5 to 3.1)	2.1 (0.2 to 23.7)	0.6 (0.1 to 8.2)	Medium
Timolol[79]	Clonidine[146, 148]	5.2 (0.2 to 111.7)	2.9 (0.4 to 19.3)	1.8 (0.1 to 66.1)	Medium
Timolol[79]	Lamotrigine[44, 87]	5.2 (0.2 to 111.7)	2.9 (0.4 to 21.6)	1.8 (0.1 to 71.2)	Medium
Timolol[79]	Tonabersat[121]	5.2 (0.2 to 111.7)	2.2 (0.2 to 25.4)	2.3 (0.1 to 115.8)	Medium
Timolol[79]	Tolfenamic Acid[202]	5.2 (0.2 to 111.7)	2.1 (0.2 to 23.7)	2.5 (0.1 to 127.8)	Medium
Divalproex[45, 46]	Naproxen sodium[237-239]	1.3 (0.5 to 3.1)	2.4 (0.3 to 16.6)	0.5 (0.1 to 4.5)	Medium
Propranolol[50, 53]	Mg[194, 195]	2.4 (0.7 to 8.5)	4.1 (0.7 to 25.7)	0.6 (0.1 to 5.4)	Medium
Divalproex[45, 46]	Metoprolol[97]	1.3 (0.5 to 3.1)	1.1 (0.1 to 18.2)	1.2 (0.1 to 22.0)	Medium

Appendix Table D162. Indirect adjusted analysis of the comparative effects on the treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (results with approved drugs and statistically significant results when off label drugs were compared with each other) (strength of evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio with Active Drug vs. Placebo (95% CI)	Odds Ratio with Control Drug vs. Placebo (95% CI)	Odds Ratio of Active vs. Control Drug (95% CI)	Risk of Bias in Body of Evidence
Timolol[79]	Naproxen sodium[237-239]	5.2 (0.2 to 111.7)	2.4 (0.3 to 16.6)	2.2 (0.1 to 82.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Mg[194, 195]	2.0 (1.4 to 2.8)	4.1 (0.7 to 25.7)	0.5 (0.1 to 3.1)	Medium
Propranolol[50, 53]	Tonabersat[121]	2.4 (0.7 to 8.5)	2.2 (0.2 to 25.4)	1.1 (0.1 to 16.5)	Medium
Propranolol[50, 53]	Tolfenamic Acid[202]	2.4 (0.7 to 8.5)	2.1 (0.2 to 23.7)	1.2 (0.1 to 18.3)	Medium
Timolol[79]	Metoprolol[97]	5.2 (0.2 to 111.7)	1.1 (0.1 to 18.2)	4.8 (0.1 to 306.0)	Medium
Propranolol[50, 53]	Clonidine[146, 148]	2.4 (0.7 to 8.5)	2.9 (0.4 to 19.3)	0.8 (0.1 to 8.1)	Medium
Propranolol[50, 53]	Lamotrigine[44, 87]	2.4 (0.7 to 8.5)	2.9 (0.4 to 21.6)	0.8 (0.1 to 9.0)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Tonabersat[121]	2.0 (1.4 to 2.8)	2.2 (0.2 to 25.4)	0.9 (0.1 to 10.2)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Tolfenamic Acid[202]	2.0 (1.4 to 2.8)	2.1 (0.2 to 23.7)	1.0 (0.1 to 11.3)	Medium
Timolol[79]	Lisuride[158]	5.2 (0.2 to 111.7)	2.7 (0.9 to 8.0)	2.0 (0.1 to 50.7)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Lamotrigine[44, 87]	2.0 (1.4 to 2.8)	2.9 (0.4 to 21.6)	0.7 (0.1 to 5.3)	Medium
Timolol[79]	Tizanidine[234]	5.2 (0.2 to 111.7)	2.1 (0.6 to 7.3)	2.4 (0.1 to 66.1)	Medium
Timolol[79]	Oxcarbazepine[83]	5.2 (0.2 to 111.7)	2.1 (0.6 to 7.3)	2.5 (0.1 to 67.6)	Medium
Timolol[79]	Bisoprolol[101]	5.2 (0.2 to 111.7)	1.8 (0.4 to 9.1)	2.9 (0.1 to 92.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Clonidine[146, 148]	2.0 (1.4 to 2.8)	2.9 (0.4 to 19.3)	0.7 (0.1 to 4.7)	Medium
Propranolol[50, 53]	Naproxen sodium[237-239]	2.4 (0.7 to 8.5)	2.4 (0.3 to 16.6)	1.0 (0.1 to 10.3)	Medium
Propranolol[50, 53]	Metoprolol[97]	2.4 (0.7 to 8.5)	1.1 (0.1 to 18.2)	2.2 (0.1 to 48.0)	Medium
Timolol[79]	Gabapentin[81, 84, 192]	5.2 (0.2 to 111.7)	2.1 (0.9 to 5.1)	2.5 (0.1 to 59.8)	Medium
Timolol[79]	Femoxetine[113, 115]	5.2 (0.2 to 111.7)	2.0 (0.5 to 7.1)	2.6 (0.1 to 73.3)	Medium
Divalproex[45, 46]	Lisuride[158]	1.3 (0.5 to 3.1)	2.7 (0.9 to 8.0)	0.5 (0.1 to 1.9)	Medium
Divalproex[45, 46]	Bisoprolol[101]	1.3 (0.5 to 3.1)	1.8 (0.4 to 9.1)	0.7 (0.1 to 4.5)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Naproxen sodium[237-239]	2.0 (1.4 to 2.8)	2.4 (0.3 to 16.6)	0.8 (0.1 to 6.0)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Metoprolol[97]	2.0 (1.4 to 2.8)	1.1 (0.1 to 18.2)	1.8 (0.1 to 30.7)	Medium
Timolol[79]	Amitriptyline[103, 111]	5.2 (0.2 to 111.7)	2.0 (1.1 to 3.9)	2.6 (0.1 to 58.9)	Medium
Divalproex[45, 46]	Tizanidine[234]	1.3 (0.5 to 3.1)	2.1 (0.6 to 7.3)	0.6 (0.1 to 2.7)	Medium
Divalproex[45, 46]	Oxcarbazepine[83]	1.3 (0.5 to 3.1)	2.1 (0.6 to 7.3)	0.6 (0.1 to 2.8)	Medium
Divalproex[45, 46]	Femoxetine[113, 115]	1.3 (0.5 to 3.1)	2.0 (0.5 to 7.1)	0.6 (0.1 to 3.0)	Medium
Timolol[79]	Montelukast[203]	5.2 (0.2 to 111.7)	0.9 (0.1 to 6.5)	5.8 (0.2 to 222.7)	Medium
Divalproex[45, 46]	Montelukast[203]	1.3 (0.5 to 3.1)	0.9 (0.1 to 6.5)	1.4 (0.2 to 12.3)	Medium
Divalproex[45, 46]	Gabapentin[81, 84, 192]	1.3 (0.5 to 3.1)	2.1 (0.9 to 5.1)	0.6 (0.2 to 2.1)	Medium
Propranolol[50, 53]	Lisuride[158]	2.4 (0.7 to 8.5)	2.7 (0.9 to 8.0)	0.9 (0.2 to 4.8)	Medium
Propranolol[50, 53]	Bisoprolol[101]	2.4 (0.7 to 8.5)	1.8 (0.4 to 9.1)	1.3 (0.2 to 10.4)	Medium
Timolol[79]	Fluoxetine[118]	5.2 (0.2 to 111.7)	1.0 (0.2 to 4.3)	5.5 (0.2 to 165.6)	Medium
Propranolol[50, 53]	Tizanidine[234]	2.4 (0.7 to 8.5)	2.1 (0.6 to 7.3)	1.1 (0.2 to 6.6)	Medium
Propranolol[50, 53]	Oxcarbazepine[83]	2.4 (0.7 to 8.5)	2.1 (0.6 to 7.3)	1.1 (0.2 to 6.7)	Medium

Appendix Table D162. Indirect adjusted analysis of the comparative effects on the treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (results with approved drugs and statistically significant results when off label drugs were compared with each other) (strength of evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio with Active Drug vs. Placebo (95% CI)	Odds Ratio with Control Drug vs. Placebo (95% CI)	Odds Ratio of Active vs. Control Drug (95% CI)	Risk of Bias in Body of Evidence
Divalproex[45, 46]	Methysergide[154]	1.3 (0.5 to 3.1)	0.5 (0.0 to 5.6)	2.5 (0.2 to 33.7)	Medium
Divalproex[45, 46]	Amitriptyline[103, 111]	1.3 (0.5 to 3.1)	2.0 (1.1 to 3.9)	0.6 (0.2 to 1.9)	Medium
Propranolol[50, 53]	Femoxetine[113, 115]	2.4 (0.7 to 8.5)	2.0 (0.5 to 7.1)	1.2 (0.2 to 7.4)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Bisoprolol[101]	2.0 (1.4 to 2.8)	1.8 (0.4 to 9.1)	1.1 (0.2 to 5.8)	Medium
Timolol[79]	Methysergide[154]	5.2 (0.2 to 111.7)	0.5 (0.0 to 5.6)	10.6 (0.2 to 525.8)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Lisuride[158]	2.0 (1.4 to 2.8)	2.7 (0.9 to 8.0)	0.7 (0.2 to 2.3)	Medium
Divalproex[45, 46]	Fluoxetine[118]	1.3 (0.5 to 3.1)	1.0 (0.2 to 4.3)	1.3 (0.2 to 7.6)	Medium
Propranolol[50, 53]	Gabapentin[81, 84, 192]	2.4 (0.7 to 8.5)	2.1 (0.9 to 5.1)	1.1 (0.2 to 5.3)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Tizanidine[234]	2.0 (1.4 to 2.8)	2.1 (0.6 to 7.3)	0.9 (0.3 to 3.3)	Medium
Propranolol[50, 53]	Montelukast[203]	2.4 (0.7 to 8.5)	0.9 (0.1 to 6.5)	2.7 (0.3 to 28.0)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Oxcarbazepine[83]	2.0 (1.4 to 2.8)	2.1 (0.6 to 7.3)	0.9 (0.3 to 3.4)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Femoxetine[113, 115]	2.0 (1.4 to 2.8)	2.0 (0.5 to 7.1)	1.0 (0.3 to 3.8)	Medium
Timolol[79]	Nimodipine[132, 133]	5.2 (0.2 to 111.7)	0.7 (0.2 to 2.7)	7.8 (0.3 to 227.8)	Medium
Propranolol[50, 53]	Amitriptyline[103, 111]	2.4 (0.7 to 8.5)	2.0 (1.1 to 3.9)	1.2 (0.3 to 4.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Montelukast[203]	2.0 (1.4 to 2.8)	0.9 (0.1 to 6.5)	2.2 (0.3 to 16.4)	Medium
Propranolol[50, 53]	Methysergide[154]	2.4 (0.7 to 8.5)	0.5 (0.0 to 5.6)	4.8 (0.3 to 74.8)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Methysergide[154]	2.0 (1.4 to 2.8)	0.5 (0.0 to 5.6)	4.0 (0.3 to 46.1)	Medium
Propranolol[50, 53]	Fluoxetine[118]	2.4 (0.7 to 8.5)	1.0 (0.2 to 4.3)	2.5 (0.4 to 17.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Gabapentin[81, 84, 192]	2.0 (1.4 to 2.8)	2.1 (0.9 to 5.1)	0.9 (0.4 to 2.4)	Medium
Divalproex[45, 46]	Nimodipine[132, 133]	1.3 (0.5 to 3.1)	0.7 (0.2 to 2.7)	1.9 (0.4 to 10.0)	Medium
Divalproex[45, 46]	Atenolol[99]	1.3 (0.5 to 3.1)	0.1 (0.0 to 2.7)	9.2 (0.4 to 206.0)	Medium
Divalproex[45, 46]	Dihydroergotamine[233]	1.3 (0.5 to 3.1)	0.1 (0.0 to 2.7)	9.4 (0.4 to 213.7)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Fluoxetine[118]	2.0 (1.4 to 2.8)	1.0 (0.2 to 4.3)	2.1 (0.4 to 9.6)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Amitriptyline[103, 111]	2.0 (1.4 to 2.8)	2.0 (1.1 to 3.9)	1.0 (0.5 to 2.0)	Medium
Timolol[79]	Atenolol[99]	5.2 (0.2 to 111.7)	0.1 (0.0 to 2.7)	38.1 (0.5 to 2739.1)	Medium
Propranolol[50, 53]	Nimodipine[132, 133]	2.4 (0.7 to 8.5)	0.7 (0.2 to 2.7)	3.6 (0.5 to 23.9)	Medium
Timolol[79]	Dihydroergotamine[233]	5.2 (0.2 to 111.7)	0.1 (0.0 to 2.7)	39.1 (0.5 to 2833.1)	Medium
Propranolol[50, 53]	Atenolol[99]	2.4 (0.7 to 8.5)	0.1 (0.0 to 2.7)	17.4 (0.7 to 446.5)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Nimodipine[132, 133]	2.0 (1.4 to 2.8)	0.7 (0.2 to 2.7)	3.0 (0.7 to 12.6)	Medium
Propranolol[50, 53]	Dihydroergotamine[233]	2.4 (0.7 to 8.5)	0.1 (0.0 to 2.7)	17.9 (0.7 to 463.0)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Atenolol[99]	2.0 (1.4 to 2.8)	0.1 (0.0 to 2.7)	14.3 (0.7 to 288.9)	Medium
Topiramate[19, 24, 28, 29, 31, 35, 42, 44]	Dihydroergotamine[233]	2.0 (1.4 to 2.8)	0.1 (0.0 to 2.7)	14.7 (0.7 to 299.8)	Medium
Dihydroergotamine[233]	Timolol[79]	0.1 (0.0 to 2.7)	5.2 (0.2 to 111.7)	0.0 (0.0 to 1.9)	Medium
Atenolol[99]	Timolol[79]	0.1 (0.0 to 2.7)	5.2 (0.2 to 111.7)	0.0 (0.0 to 1.9)	Medium
Nimodipine[132, 133]	Timolol[79]	0.7 (0.2 to 2.7)	5.2 (0.2 to 111.7)	0.1 (0.0 to 3.7)	Medium

Appendix Table D162. Indirect adjusted analysis of the comparative effects on the treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (results with approved drugs and statistically significant results when off label drugs were compared with each other) (strength of evidence is low due to risk of bias and imprecision) (continued)

Active Drug, Reference	Control Drug, Reference	Odds Ratio with Active Drug vs. Placebo (95% CI)	Odds Ratio with Control Drug vs. Placebo (95% CI)	Odds Ratio of Active vs. Control Drug (95% CI)	Risk of Bias in Body of Evidence
Methysergide[154]	Timolol[79]	0.5 (0.0 to 5.6)	5.2 (0.2 to 111.7)	0.1 (0.0 to 4.7)	Medium
Montelukast[203]	Timolol[79]	0.9 (0.1 to 6.5)	5.2 (0.2 to 111.7)	0.2 (0.0 to 6.6)	Medium
Metoprolol[97]	Timolol[79]	1.1 (0.1 to 18.2)	5.2 (0.2 to 111.7)	0.2 (0.0 to 13.4)	Medium
Fluoxetine[118]	Timolol[79]	1.0 (0.2 to 4.3)	5.2 (0.2 to 111.7)	0.2 (0.0 to 5.6)	Medium
Femoxetine[113, 115]	Timolol[79]	2.0 (0.5 to 7.1)	5.2 (0.2 to 111.7)	0.4 (0.0 to 10.5)	Medium
Oxcarbazepine[83]	Timolol[79]	2.1 (0.6 to 7.3)	5.2 (0.2 to 111.7)	0.4 (0.0 to 11.0)	Medium
Bisoprolol[101]	Timolol[79]	1.8 (0.4 to 9.1)	5.2 (0.2 to 111.7)	0.3 (0.0 to 11.0)	Medium
Naproxen sodium[237-239]	Timolol[79]	2.4 (0.3 to 16.6)	5.2 (0.2 to 111.7)	0.5 (0.0 to 17.1)	Medium
Tolfenamic Acid[202]	Timolol[79]	2.1 (0.2 to 23.7)	5.2 (0.2 to 111.7)	0.4 (0.0 to 19.8)	Medium
Tonabersat[121]	Timolol[79]	2.2 (0.2 to 25.4)	5.2 (0.2 to 111.7)	0.4 (0.0 to 21.4)	Medium
Lamotrigine[44, 87]	Timolol[79]	2.9 (0.4 to 21.6)	5.2 (0.2 to 111.7)	0.6 (0.0 to 21.6)	Medium
Carbamazepine[86]	Timolol[79]	3.1 (0.1 to 77.1)	5.2 (0.2 to 111.7)	0.6 (0.0 to 50.2)	Medium
Amitriptyline[103, 111]	Timolol[79]	2.0 (1.1 to 3.9)	5.2 (0.2 to 111.7)	0.4 (0.0 to 8.9)	Medium
Gabapentin[81, 84, 192]	Timolol[79]	2.1 (0.9 to 5.1)	5.2 (0.2 to 111.7)	0.4 (0.0 to 9.8)	Medium
Tizanidine[234]	Timolol[79]	2.1 (0.6 to 7.3)	5.2 (0.2 to 111.7)	0.4 (0.0 to 11.1)	Medium
Lisuride[158]	Timolol[79]	2.7 (0.9 to 8.0)	5.2 (0.2 to 111.7)	0.5 (0.0 to 13.2)	Medium
Clonidine[146, 148]	Timolol[79]	2.9 (0.4 to 19.3)	5.2 (0.2 to 111.7)	0.6 (0.0 to 20.4)	Medium
Mg[194, 195]	Timolol[79]	4.1 (0.7 to 25.7)	5.2 (0.2 to 111.7)	0.8 (0.0 to 28.0)	Medium
Pindolol[89]	Timolol[79]	7.8 (0.4 to 158.9)	5.2 (0.2 to 111.7)	1.5 (0.0 to 110.0)	Medium
Nifedipine[129]	Timolol[79]	6.1 (0.6 to 56.4)	5.2 (0.2 to 111.7)	1.2 (0.0 to 51.3)	Medium
Acetazolamide[80]	Timolol[79]	6.6 (1.3 to 34.5)	5.2 (0.2 to 111.7)	1.3 (0.0 to 41.2)	Medium
Dihydroergotamine[233]	Acetazolamide[80]	0.1 (0.0 to 2.7)	6.6 (1.3 to 34.5)	0.0 (0.0 to 0.6)	Medium
Atenolol[99]	Acetazolamide[80]	0.1 (0.0 to 2.7)	6.6 (1.3 to 34.5)	0.0 (0.0 to 0.6)	Medium
Dihydroergotamine[233]	Nifedipine[129]	0.1 (0.0 to 2.7)	6.1 (0.6 to 56.4)	0.0 (0.0 to 0.9)	Medium
Atenolol[99]	Nifedipine[129]	0.1 (0.0 to 2.7)	6.1 (0.6 to 56.4)	0.0 (0.0 to 0.9)	Medium
Nimodipine[132, 133]	Acetazolamide[80]	0.7 (0.2 to 2.7)	6.6 (1.3 to 34.5)	0.1 (0.0 to 0.9)	Medium
Nifedipine[129]	Atenolol [99]	6.1 (0.6 to 56.4)	0.1 (0.0 to 2.7)	44.2 (1.1 to 1831.0)	Medium
Nifedipine[129]	Dihydroergotamine[233]	6.1 (0.6 to 56.4)	0.1 (0.0 to 2.7)	45.4 (1.1 to 1896.0)	Medium
Acetazolamide[80]	Nimodipine[132, 133]	6.6 (1.3 to 34.5)	0.7 (0.2 to 2.7)	9.9 (1.1 to 86.8)	Medium
Acetazolamide[80]	Atenolol[99]	6.6 (1.3 to 34.5)	0.1 (0.0 to 2.7)	48.3 (1.6 to 1459.9)	Medium
Acetazolamide[80]	Dihydroergotamine[233]	6.6 (1.3 to 34.5)	0.1 (0.0 to 2.7)	49.6 (1.6 to 1513.0)	Medium

Table D163. Exploratory network Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials

Active Class	Active Drug	Control Class	Control Drugs	Risk of Bias Reference	Events/ Randomized In Active	Events/ Randomized In Control	Events/ Randomized In Control
Antidepressant	Amitriptyline	Ergot alkaloid	Dihydroergotamine	Medium Bonuso, 1983[159]	3/21	2/20	NA/1
Antiepileptic	Topiramate	Antidepressant	Amitriptyline	Medium Keskinbora, 2008[170]	2/24	4/28	NA/1
Antiepileptic	Topiramate	Antidepressant	Amitriptyline	Low Dodick, 2009[172]	35/178	38/169	NA/1
Antiepileptic	Divalproex	Beta blocker	Propranolol	High Kaniecki, 1997[68]	4/37	1/37	NA/1
Antiepileptic	Valproate	Calcium-channel antagonist	Cinnarizine	Low Togha, 2008[190]	3/58	2/67	NA/1
Antiepileptic	Topiramate		Histamine	Low Millan-Guerrero, 2008[169]	10/45	0/45	NA/1
Anti-epileptic	Topiramate	Anti-epileptic	Levetiracetam	Medium de Tommaso, 2007[168]	1/13	0/15	NA/1
Beta blocker	Propranolol	Antidepressant	Femoxetine	Medium Kangasniemi, 1983[77]	0/29	3/29	NA/1
Beta-blocker	Metoprolol	Antiadrenergics	Clonidine	Medium Louis, 1985[183]	0/31	4/31	NA/1
Beta-blocker	Propranolol	Antidepressant Ergot alkaloid	Amitriptyline, Ergotamine	High Mathew, 1981[105]	3/48	3/44	9/49
Beta-blocker	Metoprolol	Anti-depressant	Clomipramine	Medium Langohr, 1985[184]	0/63	18/63	NA/1
Beta-blocker	Propranolol Hydrochloride	Beta blocker	Nadolol	Medium Sudilovsky, 1987[191]	4/44	2/47	NA/1
Beta-blocker	Propranolol	Dopaminergic agent	Dihydroergocryptine	High Micieli, 2001[244]	5/20	4/20	NA/1
Beta-blocker	Propranolol	Selective calcium channel blockers	Nifedipine	High Albers, 1989[74]	5/20	13/20	NA/1
Placebo	Placebo	Antiadrenergics	Clonidine	Medium Adam, 1978[148]	1/96	2/96	NA/1
Placebo	Placebo	Antiadrenergics	Clonidine	Medium Boisen, 1978[146]	0/71	2/71	NA/1
Placebo	Placebo	Antidepressant	Amitriptyline	Medium Couch, 1979[103]	2/61	5/55	NA/1

Table D163. Exploratory network Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (continued)

Active Class	Active Drug	Control Class	Control Drugs	Risk of Bias Reference	Events/ Randomized In Active	Events/ Randomized In Control	Events/ Randomized In Control
Placebo	Placebo	Antidepressant	Amitriptyline	Medium Couch, 2011[111]	13/197	23/194	NA/1
Placebo	Placebo	Antidepressant	Femoxetine	Medium Orholm, 1986[113]	2/34	4/31	NA/1
Placebo	Placebo	Antidepressant	Femoxetine	Medium Orholm, 1985[115]	2/30	3/29	NA/1
Placebo	Placebo	Antidepressant	Fluoxetine,	High Steiner, 1998[118]	4/26	4/27	NA/1
Placebo	Placebo	Antiepileptic	Acetazolamide	Low Vahedi, 2002[80]	2/27	9/26	NA/1
Placebo	Placebo	Antiepileptic	Carbamazepine	Medium Rompel, 1970[86]	0/48	1/48	NA/1
Placebo	Placebo	Antiepileptic	Divalproex	Medium Mathew, 1995[45]	2/37	9/70	NA/1
Placebo	Placebo	Antiepileptic	Divalproex	Low Freitag, 2002[46]	10/116	10/123	NA/1
Placebo	Placebo	Antiepileptic	Gabapentin	Medium Mathew, 2001[81]	4/45	16/98	NA/1
Placebo	Placebo	Antiepileptic	Gabapentin	Medium Wessely, 1987[84]	1/22	2/23	NA/1
Placebo	Placebo	Antiepileptic	Gabapentin enacarbil	Low NCT00742209[192]	2/20	13/62	NA/1
Placebo	Placebo	Antiepileptic	Lamotrigine	Low Steiner, 1997[87]	3/40	7/18	NA/1
Placebo	Placebo	Antiepileptic	Oxcarbazepine	Low Silberstein, 2008[83]	4/85	8/85	NA/1
Placebo	Placebo	Antiepileptic	Sodium valproate	Medium Jensen, 1994[49]	2/43	4/43	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Medium Mei, 2004[24]	2/57	3/58	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Low Mei, 2006[28]	6/20	9/30	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Medium Silberstein, 2006[29]	4/73	21/140	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Low Silberstein, 2007[31]	10/163	18/165	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Low Lainez, 2007[35]	41/383	96/391	NA/1

Table D163. Exploratory network Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (continued)

Active Class	Active Drug	Control Class	Control Drugs	Risk of Bias Reference	Events/ Randomized In Active	Events/ Randomized In Control	Events/ Randomized In Control
Placebo	Placebo	Antiepileptic	Topiramate	Low Lipton, 2011[42]	18/197	21/188	NA/1
Placebo	Placebo	Antiepileptic	Topiramate	Low Edwards, 2003[19]	0/36	6/34	NA/1
Placebo	Placebo	Antiepileptic	Valproate	Medium Hering, 1992[48]	2/32	1/32	NA/1
Placebo	Placebo	Antiepileptic Antiepileptic	Topiramate, Lamotrigine	Low Gupta, 2007[44]	3/60	3/60	3/60
Placebo	Placebo	Beta-blocker	Atenolol	Medium Johannsson, 1987[99]	3/72	0/72	NA/1
Placebo	Placebo	Beta-blocker	Bisoprolol	Medium van de Ven, 1997[101]	2/38	7/77	NA/1
Placebo	Placebo	Beta-blocker	Metoprolol	Medium Andersson, 1983[97]	1/37	1/34	NA/1
Placebo	Placebo	Beta-blocker	Pindolol	Medium Sjaastad, 1972[89]	0/28	3/28	NA/1
Placebo	Placebo	Beta-blocker	Propranolol	Medium Diamond, 1976[50]	1/83	6/83	NA/1
Placebo	Placebo	Beta-blocker	Timolol	Medium Stellar, 1984[79]	0/47	2/47	NA/1
Placebo	Placebo	Beta-blocker	Propranolol	Low Pradalier, 1989[53]	5/24	9/31	NA/1
Placebo	Placebo	Ergot alkaloid	Dihydroergotamine	Medium Bousser, 1988[233]	3/45	0/45	NA/1
Placebo	Placebo	Ergot alkaloids	Lisuride	Medium Somerville, 1976[158]	5/75	12/75	NA/1
Placebo	Placebo	Ergot alkaloids	Methysergide	Medium Whewell, 1966[154]	2/74	1/74	NA/1
Placebo	Placebo	Magnesium	Magnesium	Low Peikert, 1996[195]	0/38	3/43	NA/1
Placebo	Placebo	Magnesium	Magnesium	Low Pfaffenrath, 1996[194]	1/34	3/35	NA/1
Placebo	Placebo	Muscle relaxant	Tizanidine	Medium Saper, 2002[234]	4/64	9/72	NA/1
Placebo	Placebo	NSAID	Naproxen sodium	High Ziegler, 1985[239]	0/40	1/40	NA/1
Placebo	Placebo	NSAID	Naproxen sodium	High Welch, 1985[237, 238]7068	1/46	2/46	NA/1

Table D163. Exploratory network Bayesian meta-analysis of treatment discontinuation due to bothersome adverse effects with preventive drugs in adults, results from randomized controlled clinical trials (continued)

Active Class	Active Drug	Control Class	Control Drugs	Risk of Bias Reference	Events/ Randomized In Active	Events/ Randomized In Control	Events/ Randomized In Control
Placebo	Placebo	NSAID	Tolfenamic Acid	Medium Mikkelsen, 1982[202]	1/38	2/38	NA/1
Placebo	Placebo	Other	Tonabersat	Low Goadsby, 2009[121]	1/65	2/59	NA/1
Placebo	Placebo	Selective calcium channel blockers	Nifedipine	High McArthur, 1989[129]	1/24	5/24	NA/1
Placebo	Placebo	Selective calcium channel blockers	Nimodipine	Low MINES, 1989[133]	4/46	3/43	NA/1
Placebo	Placebo	Selective calcium channel blockers	Nimodipine	Medium Havanka-Kanniainen, 1985[132]	1/33	0/33	NA/1
Placebo	Placebo	Systemic Drugs	Montelukast	Low Brandes, 2004[203]	2/84	2/93	NA/1

Bold = significant differences at 95% confidence limit when 95% CI of odds ratio estimates do not include 1

Appendix Table D164. Decrease in frequency of migraine >50% with amitriptyline vs. placebo in adults with different baseline migraine frequency, results from medium risk of bias RCT[111]

Baseline Migraine Frequency	Weeks of Treatment	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Baseline ≥17 Headaches per month	4	5.5 (0.7 to 40.5)	**0.20 (0.04 to 0.37)**
Baseline 1-16 Headaches per month	4	0.7 (0.3 to 1.5)	-0.04 (-0.10 to 0.03)
Baseline ≥17 Headaches per month	8	1.7 (0.5 to 5.4)	0.14 (-0.12 to 0.39)
Baseline 1-16 Headaches per month	8	1.0 (0.5 to 2.2)	0.00 (-0.08 to 0.08)
Baseline ≥17 Headaches per month	12	5.0 (0.7 to 34.3)	**0.37 (0.11 to 0.63)**
Baseline 1-16 Headaches per month	12	1.2 (0.6 to 2.5)	0.02 (-0.08 to 0.12)
Baseline ≥17 Headaches per month	16	1.8 (0.5 to 7.1)	0.16 (-0.16 to 0.48)
Baseline 1-16 Headaches per month	16	0.8 (0.4 to 1.8)	-0.03 (-0.13 to 0.07)

Bold = significant difference at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0
CI = confidence interval

Appendix Table D165. Improvement of M score >50%* with amitriptyline vs. placebo in adults with different baseline M score and depressive symptoms, results from medium risk of bias RCT[103]

Baseline Condition	Relative Risk (95% CI)	Absolute Risk Difference (95% CI)
Baseline H<14	1.6 (1.0 to 2.5)	0.21 (0.00 to 0.43)
Baseline H>=14	1.5 (0.4 to 5.7)	0.13 (-0.29 to 0.54)
Baseline M<100	1.7 (0.9 to 3.0)	0.21 (-0.01 to 0.43)
Baseline M<100 AND H<14	1.5 (0.8 to 2.8)	0.16 (-0.08 to 0.40)
Baseline M<100 AND H>14	3.0 (0.8 to 11.3)	0.50 (-0.02 to 1)
Baseline M≥100	1.4 (0.7 to 2.9)	0.21 (-0.18 to 0.59)
Baseline M≥100 AND H<14	**1.7 (1.0 to 3.1)**	**0.44 (0.10 to 0.79)**
Baseline M≥100 AND H>14	0.3 (0.0 to 6.4)	-0.25 (-0.73 to 0.23)

M score = 2 (frequency*duration) Disabling+1 (frequency*duration) Severe; H SCORE=Hamilton Physician Depression Rating Scale (0-7 normal, 20 - severe depression)

Bold = significant difference at 95% confidence limit when 95% CI of relative risk estimates do not include 1 and 95% CI of absolute risk difference estimates do not include 0

CI = confidence interval

Appendix Table D166. Prediction of ≥50% in migraine days reduction per month with different doses of amitriptyline (50 vs. 25mg/day) for migraine prevention in adults, results from medium risk of bias RCT[110]

Predictor of Effect	Odds Ratio (95% CI)
Age (+1 year)	1.08 (0.99 to 1.17)
Age at onset of migraine (+1 year)	1.04 (0.94 to 1.16)
Amitriptyline ER 50 mg per day (versus not)	0.24 (0.06 to 1.04)
Duration of attack (+1 h)	1.04 (0.98 to 1.12)
Male gender (versus female)	2.1 (0.45 to 9.87)
Migraine days per month (+1 day)	**2.35 (1.45 to 3.8)**
Migraine with aura (versus without)	0.63 (0.13 to 3.12)
Number of drugs (+1 drug)	1.02 (0.67 to 1.55)
Pain intensity per attack (+1 score point)	0.69 (0.46 to 1.04)
Positive family history of migraine (versus negative)	2.35 (0.57 to 9.72)
Smoker (versus not)	2.23 (0.44 to 11.3)

Bold = significant difference at 95% confidence limit when 95% CI of odds ratio estimates do not include 1
CI = confidence interval

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