



# Effective Health Care Program

## Migraine in Adults: Preventive Pharmacologic Treatments

### 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.<sup>1,2</sup> Migraine headaches range from moderate to very severe<sup>3</sup> and are sometimes debilitating.<sup>4</sup> Episodic migraine affects 17 percent of women and 6 percent of men.<sup>5-8</sup>

Migraine frequency is divided into episodic and chronic.<sup>2</sup> Episodic migraine is characterized by <15 migraine days and chronic migraine by  $\geq 15$  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.<sup>9</sup> 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.<sup>10</sup>

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.<sup>5</sup> Preventive medications from several drug classes

#### Effective Health Care Program

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

The full report and this summary are available at [www.effectivehealthcare.ahrq.gov/reports/final.cfm](http://www.effectivehealthcare.ahrq.gov/reports/final.cfm).

are thought to affect various aspects of migraine pathophysiology.<sup>11,12</sup> The U.S. Food and Drug Administration (FDA) has approved four drugs for *episodic* migraine prevention in adults: the beta



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blockers propranolol and timolol, and the antiepileptic drugs topiramate and divalproex sodium.<sup>13</sup> 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.<sup>13</sup>

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  $\geq 50$  percent.<sup>3</sup> Preventive treatments are also expected to reduce use of acute drugs and improve quality of life.<sup>6</sup> 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.<sup>14,15</sup> 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.<sup>16</sup> 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.<sup>17,18</sup> Often, preventive treatment is recommended for only 6 to 9 months; however, very limited research has examined migraine frequency after discontinuation of preventive treatments.<sup>3,19</sup>

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.<sup>20</sup> 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.<sup>20,21</sup>

## 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).<sup>22</sup> 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<sup>23,24</sup> and PRISMA guidelines (protocol registration number is CRD42012001918, available at [www.crd.york.ac.uk/prospero/display\\_record.asp?ID=CRD42012001918](http://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.<sup>25</sup> 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.<sup>26</sup> We defined harms as the totality of all possible adverse consequences of an intervention.<sup>27</sup> We analyzed harms regardless of how authors perceived causality of treatments.

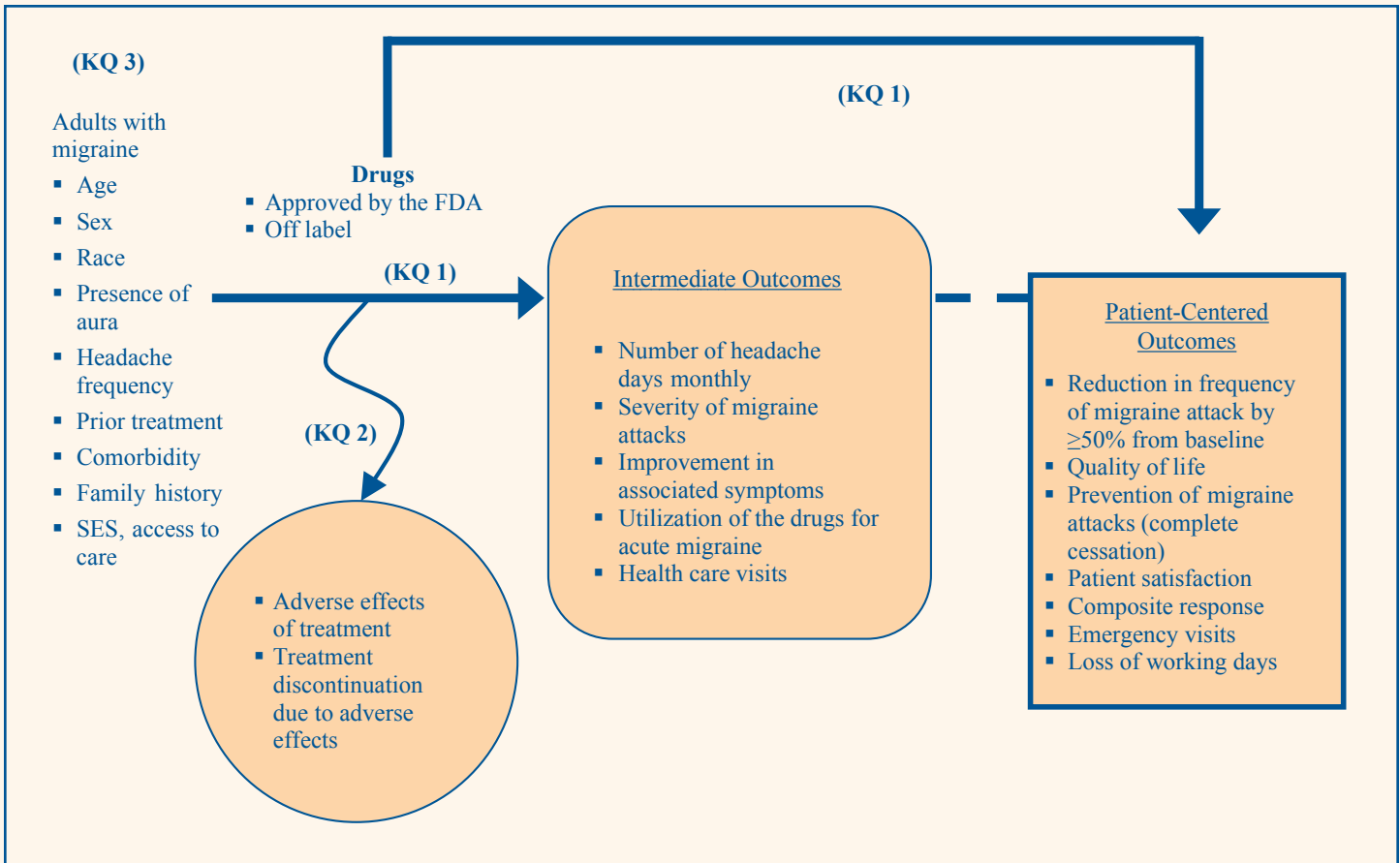
We determined eligibility according to the PICOTS (Population, Intervention, Comparator, Outcomes, Timing, and Settings) framework. We defined the target population as community-dwelling adults with episodic or chronic migraine. We formulated a list of eligible interventions after discussions with key 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.<sup>17</sup> 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](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.<sup>28</sup> 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  $\geq 50$  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.<sup>17</sup> 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.<sup>29</sup> 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<sup>®</sup> 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  $\geq 50$  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.<sup>30</sup> 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  $\geq 300$  events (using 25% relative effect difference for calculation of optimal information size).<sup>31</sup> 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  $>5$ .<sup>25</sup> 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.<sup>32</sup>

## 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.

### **KQ 1a. 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  $\geq 50$  percent in patients with baseline  $\geq 15$  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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  percent (Table A).

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  $\geq 50$  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  $\geq 50$  percent.

Individual RCTs of angiotensin inhibiting drugs demonstrated promising results. The angiotensin

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

<b>Active Preventive Treatment</b>	<b>Outcome</b>	<b>Sample</b>	<b>Rate, Percent With Drug [Placebo]</b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Risk Difference (95% CI)</b>	<b>Number Needed To Treat (95% CI)</b>	<b>Attributable Events per 1,000 Treated (95% CI)</b>	<b>Strength of Evidence (Reasons for Lowering SOE)</b>
<b>Onabotulinumtoxin A for chronic migraine</b>	≥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)
<b>Topiramate 50 to 200mg for episodic migraine</b>	≥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)
<b>Topiramate 50 to 200mg/day for episodic migraine</b>	≥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)
<b>Divalproex</b> 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)
<b>Propranolol</b> 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)
<b>Timolol</b> 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)



**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)
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)
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.

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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  percent.

### **QK 1b. 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.

### **Comparative Effectiveness of Approved Drugs on Prevention of Episodic Migraine**

Pooled analyses demonstrated that decrease in headache frequency by  $\geq 50$  percent did not differ with propranolol versus timolol or versus metoprolol (Table B). Propranolol was better than nifedipine in reducing monthly headache intensity by  $\geq 50$  percent. Indirect adjusted analysis demonstrated no differences among approved drugs in reducing monthly headache frequency by  $\geq 50$  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  $\geq 50$  percent (Figure B).

### **QK 1c. 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  $\geq 25$  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  $\geq 50$  percent did not differ between exercising for 40 minutes three times a week, relaxation technique, or daily topiramate use.

### **QK 1d. 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.

### **QK 1e1. 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.

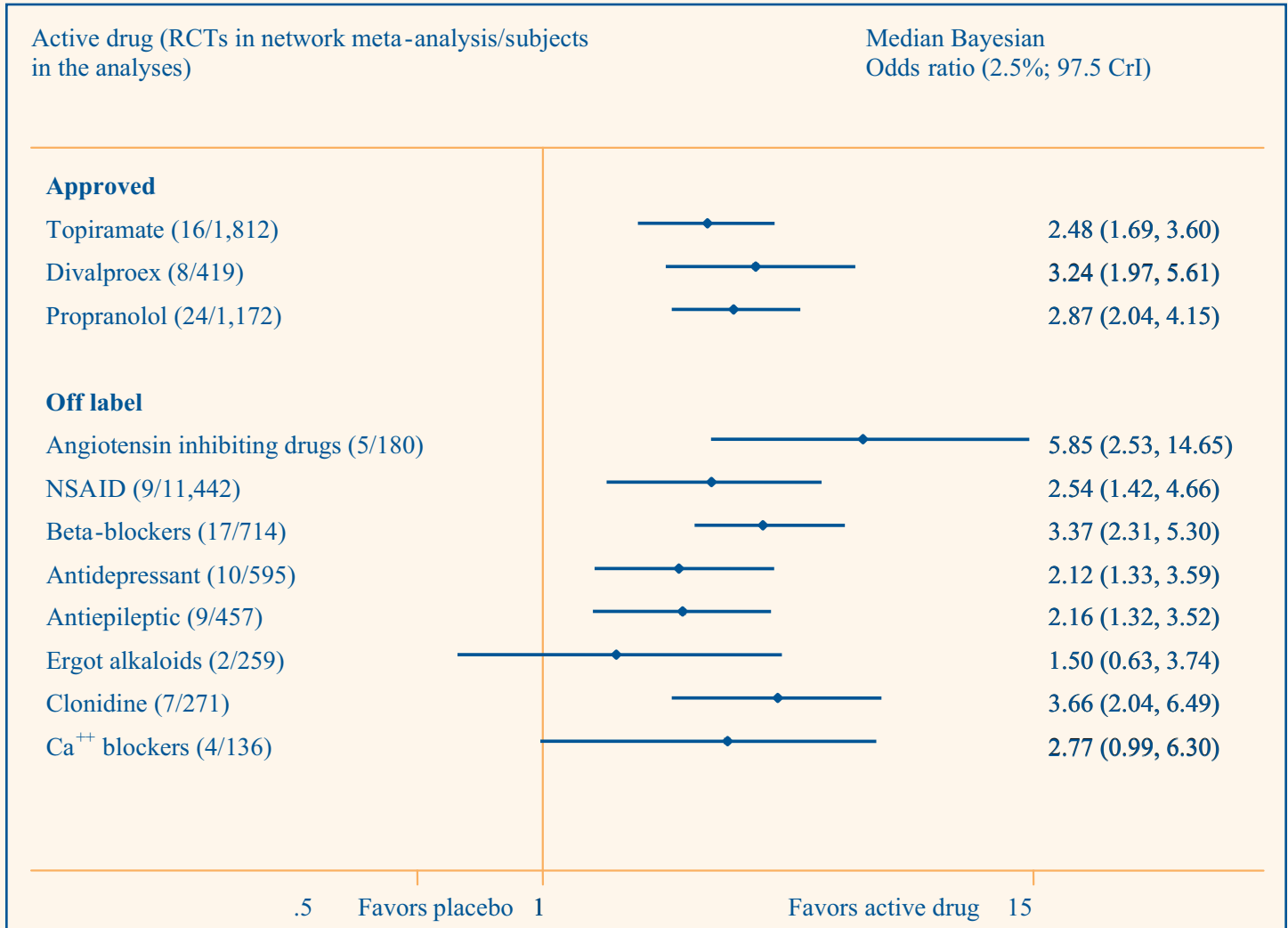
**Table B. Comparative effectiveness with migraine preventive drugs in adults, direct evidence from head-to-head randomized controlled clinical trials**

<b>Active Preventive Treatment</b>	<b>Outcome</b>	<b>Sample</b>	<b>Rate, Percent With Active [Control] Drug</b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Risk Difference (95% CI)</b>	<b>Number Needed To Treat (95% CI)</b>	<b>Attributable Events per 1,000 Treated (95% CI)</b>	<b>Strength of Evidence (Reasons for Lowering SOE)</b>
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)
<b>Propranolol vs. Nifedipine</b>	<b>≥50% decrease in migraine frequency</b>	<b>76</b>	<b>46.2 [18.9]</b>	<b>2.3 (1.1 to 4.6)</b>	<b>0.27 (0.09 to 0.46)</b>	<b>4 (2 to 11)</b>	<b>274 (89 to 458)</b>	<b>Low (high ROB, imprecision)</b>
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.

**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  $\geq 50\%$  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).

**KQ 1e2. 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.

### **KQ 2a. 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).

### **KQ 2b. 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,

**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)
<i>Compared With Placebo</i>							
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)

<b>Table C. Treatment discontinuation due to adverse effects with migraine preventive drugs in adults, evidence from meta-analyzed randomized controlled clinical trials (continued)</b>							
<b>Active Preventive Treatment</b>	<b>Sample</b>	<b>Rate, Percent With Active Drug [Control]</b>	<b>Relative Risk (95% CI)</b>	<b>Absolute Risk Difference (95% CI)</b>	<b>Number Needed To Treat (95% CI)</b>	<b>Attributable Events per 1,000 Treated (95% CI)</b>	<b>Strength of Evidence (Reasons for Lowering SOE)</b>
<i>Compared With Placebo (continued)</i>							
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)
<i>Compared With Active Treatment</i>							
Topiramate vs. amitriptyline	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.

off-label angiotensin inhibiting drugs and beta-blockers were the safest treatment option for adults with episodic migraine.

**KQ 2c. 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.

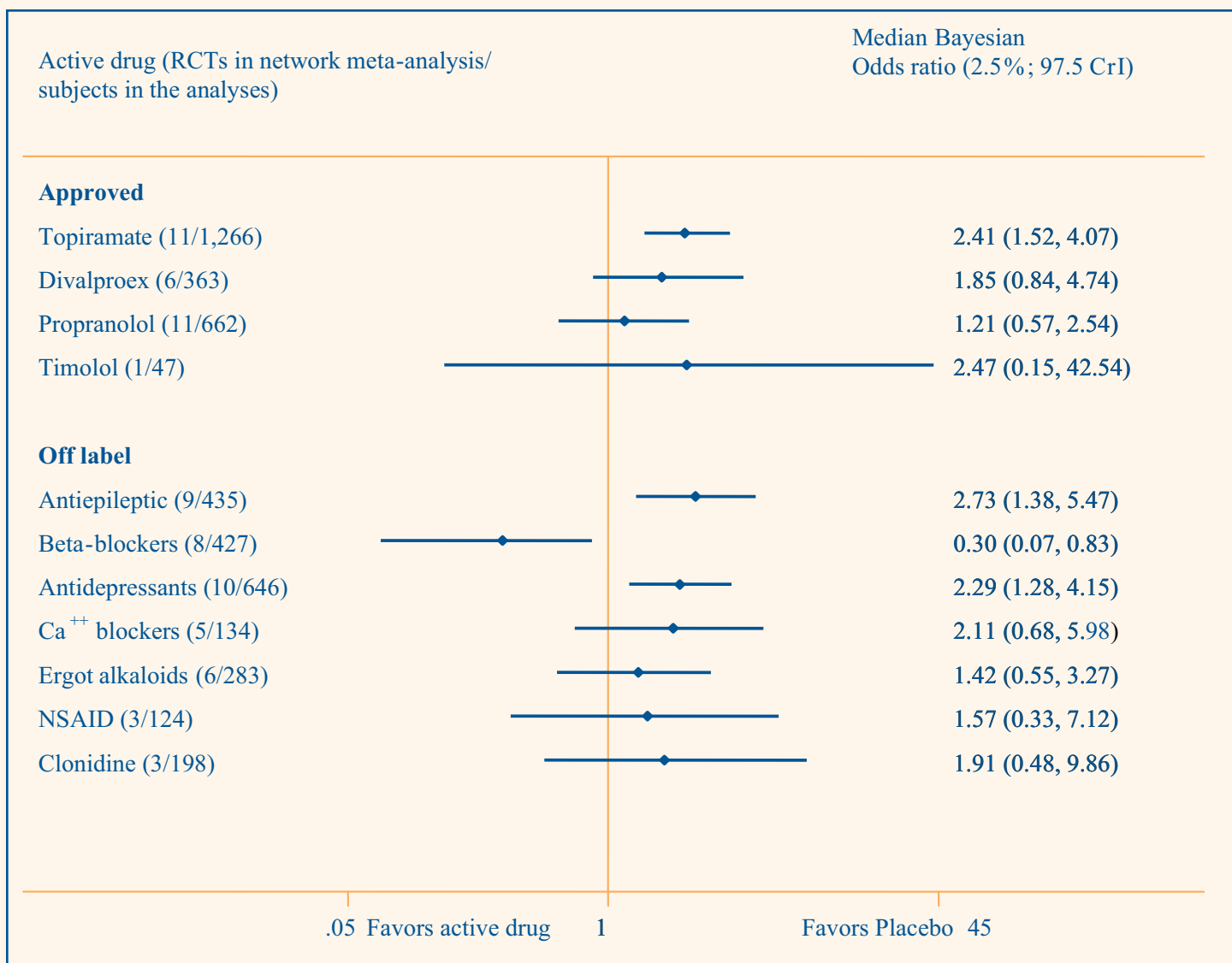
**KQ 3. Which patient characteristics predict the effectiveness and safety of pharmacological treatments for preventing migraine attacks in adults?**

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

**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



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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  percent (clinical response). The relative effect size of drugs was moderate: drugs would result in to 200 to 400 cases of clinical response ( $\geq 50$  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.<sup>33</sup> 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.<sup>34</sup> 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).<sup>35,36</sup> 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  $\geq 15$  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.<sup>15</sup> 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.<sup>37</sup> 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.<sup>38</sup>

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 decisionmaking.<sup>39</sup> 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.<sup>40</sup> 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.<sup>41</sup> 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.<sup>42,43</sup> 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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  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 to 100 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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  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  $\geq 50$  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

## **References**

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## Full Report

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