REVIEWS

Preventive Pharmacologic Treatments for Episodic Migraine in Adults

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OBJECTIVES: Systematic review of preventive pharmacologic treatments for community-dwelling adults with episodic migraine.

DATA SOURCES: Electronic databases through May 20, 2012.

ELIGIBILITY CRITERIA: English-language randomized controlled trials (RCTs) of preventive drugs compared to placebo or active treatments examining rates of ≥50 % reduction in monthly migraine frequency or improvement in quality of life.

STUDY APPRAISAL AND SYNTHESIS METHODS: We assessed risk of bias and strength of evidence and conducted random effects meta-analyses of absolute risk differences and Bayesian network meta-analysis.

RESULTS: Of 5,244 retrieved references, 215 publications of RCTs provided mostly low-strength evidence because of the risk of bias and imprecision. RCTs examined 59 drugs from 14 drug classes. All approved drugs, including topiramate (9 RCTs), divalproex (3 RCTs), timolol (3 RCTs), and propranolol (4 RCTs); off-label beta blockers metoprolol (4 RCTs), atenolol (1 RCT), nadolol (1 RCT), and acebutolol (1 RCT); angiotensin-converting enzyme inhibitors captopril (1 RCT) and lisinopril (1 RCT); and angiotensin II receptor blocker candesartan (1 RCT), outperformed placebo in reducing monthly migraine frequency by ≥50 % in 200–400 patients per 1,000 treated. Adverse effects leading to treatment discontinuation (68 RCTs) were greater with topiramate, off-label antiepileptics, and antidepressants than with placebo. Limited direct evidence as well as frequentist and exploratory network Bayesian meta-analysis showed no statistically significant differences in benefits between approved drugs. Off-label angiotensin-inhibiting drugs and beta-blockers were most effective and tolerable for episodic migraine prevention.

LIMITATIONS: We did not quantify reporting bias or contact principal investigators regarding unpublished trials.

CONCLUSIONS: Approved drugs prevented episodic migraine frequency by ≥50 % with no statistically significant difference between them. Exploratory network meta-analysis suggested that off-label angiotensin-inhibiting drugs and beta-blockers had favorable benefit-to-harm ratios. Evidence is lacking for long-term effects of drug treatments (i.e., trials of more than 3 months duration), especially for quality of life.

KEY WORDS: migraine; evidence based medicine; adverse drug effects.
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INTRODUCTION

Migraine headaches ranging from moderate to very severe[1–3] affect 17 % of women and 6 % of men.[4–7] The National Headache Foundation defined migraine as episodic (<15) or chronic (≥15 days per month for at least 3 months).[8–10] Many adults with episodic migraine experience serious lifestyle restrictions[11–13] and need preventive medications.[5,14,15] The US Food and Drug Administration (FDA) has approved four drugs for *episodic* migraine prevention in adults: two beta blockers (propranolol and timolol) and two antiepileptic drugs (topiramate and divalproex sodium).[16] Doctors also prescribe off-label drugs from other classes.[16,17]

Preventive treatments aim to reduce headache frequency by at least 50 %[18–20] without intolerable harms.[21,22] In clinical practice, physicians and patients choose preventive treatments based primarily on FDA approval and drug tolerability.[9,18,19,23–25] Systematic reviews and meta-analyses with consistent and transparent appraisal of study quality and strength of evidence are essential for arriving at evidence-based migraine preventive treatment and policy decisions.[26]

Previously published systematic reviews focused on the efficacy of specific drugs rather than comparative effectiveness

and tolerability of all pharmacologic options.[27,28] In addition, the Institute of Medicine recommends basing treatment decisions on post-marketing studies tracking drug benefits and harms after FDA approval.[29–31] Thus, we conducted a systematic literature review of the comparative effectiveness and tolerability of the available preventive medications for episodic migraine in adults in outpatient settings to inform treatment and policy decisions (CRD42012001918).[32,33] The topic, research questions, and eligible interventions were nominated and posted for public comments on the Effective Healthcare website. We chose not to synthesize studies of the drug flunarizine (commonly used for adults in Europe) because the FDA has not approved it. Efficacy of nonpharmacologic preventive treatments and prevention of chronic migraine are beyond the scope of this paper.

METHODS

Data Sources and Searches. We searched databases including MEDLINE®, the Cochrane Library, the FDA website, and the World Health Organization International Clinical Trials Registry portal to find English publications through May 20, 2012 (online Appendix Table 1).

Study Selection. Three investigators determined study eligibility. Each title and abstract was reviewed by at least two investigators, and disagreements were resolved through discussion. 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 migraine (online Appendix Table 2).[9] We formulated a list of eligible pharmacologic classes available in the US.[34] We defined eligible patient-centered outcomes (≥50 % reduction in frequency of migraine attack from baseline, complete cessation of migraine attacks, migraine-related disability, and quality of life).

We excluded studies of treatments for acute attacks, prevention of menstrual migraines or migraine variants, and studies in inpatient settings.[8,35,36]

We analyzed the effectiveness of drugs from RCTs, adverse effects, and treatment discontinuation due to adverse effects from RCTs and nonrandomized studies.[37] We defined harms as the totality of all possible adverse consequences of an intervention regardless of how authors perceived causality of treatments.[38]

Data Extraction. For each trial, one reviewer extracted the data and a second reviewer checked the abstracted data for accuracy using standardized forms (available at https://netfiles.umn.edu/xythoswfs/webui/_xy-21041343_1-t_zdhvSpvy).

We abstracted the information relevant to the PICOTS framework and minimum data sets to reproduce the results presented by the authors.

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.[39]

Risk of Bias Assessment. We evaluated the risk of bias in individual studies of benefits and harms according to: (1) random allocation of subjects to the treatment groups; (2) masking 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) planned and executed intention-to-treat principles; and 6) selective outcome reporting when compared with the articles' protocols (when available) and methods sections.[40] 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 risk-of-bias criteria, a medium risk of bias if one criterion was not met, and a high risk of bias if two or more 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: (1) adjustment for confounding factors to address selection biases and (2) 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. Incorporating risk of bias of individual studies into the synthesis of evidence, we used individual risk of bias criteria rather than a global score.[41,42]

Data Synthesis and Analysis. Using Meta-Analyst[43] and STATA®[44] software at a 95 % confidence level, we calculated the relative risk and absolute risk difference from the abstracted events using default software continuity correction coefficients for 0 events.[39] We hypothesized superiority of drugs versus placebo and versus each other.[45]

We pooled results only from studies that used the same active drug treatments and comparators and the same definitions of outcomes.

Many FDA-regulated and post-marketing trials were not powered to detect statistically significant increases in harms with migraine preventive drugs. We used meta-analysis of RCTs for evaluating drug safety based on all available trials.[46] We analyzed sparse adverse effects data with various statistical methods[43,47–51] for robustness by comparing statistical significance and magnitude of the harms. In cases of multi-arm trials, we created a single pair-wise comparison.[40] To avoid the spurious increase in precision in multiarm trials, we divided

placebo arms approximately evenly among the comparisons according to the randomization ratio.[39,52]

We tested consistency of the results by comparing the direction and strength of the association,[53] assessed heterogeneity in results with the chi-squared and I-squared tests,[54,55] and explored it with meta-regression and sensitivity analysis, reporting only the results from random effects models,[56] which incorporate inevitable differences between trials in patient populations, baseline rates of the outcomes, dosages of drugs, and other factors.[47] We examined whether the definition of migraine could contribute to differences in trial results. The FDA had 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.[9] Eligible studies published earlier defined classic or common migraine as per the Ad Hoc Committee on Classification of Headache.[57]

We calculated the number needed to treat to achieve one event as the reciprocal of absolute risk differences (ARD) in rates of outcome events in active and control groups.[44,58,59] 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 where very few studies provided evidence from head-to-head comparisons, we conducted indirect comparisons using statistical techniques to estimate the treatment effects from studies of each given treatment against controls under an assumption of consistency.[60–64] First, we used adjusted indirect frequentist comparisons for individual drugs compared with placebo.[62] This analysis provided pairwise triangular comparisons for drugs compared with placebo rather than network meta-analysis. Second, to address the problems with inevitable differences across studies, we used mixed (or multiple) treatment comparison (MTCs) Bayesian network meta-analysis.[62–64] We calculated Bayesian odds ratios[43,51] with 2.5 to 97.5 % credible intervals and Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments (online Appendix Table 3).[65] 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 the consistency of the estimates.[66] We concluded no differences in drug effect (hereafter called similar effects) if confidence or credible intervals included one (no effect or no difference).[67] All Bayesian results were obtained from the WinBUGS software[68] using Markov chain Monte Carlo (MCMC) samples after a 50,000-sample algorithm burn-in.

Grading the Evidence for Each Key Question. We assessed strength of evidence according to risk of bias, consistency, directness, and precision for clinical response and treatment discontinuation due to harms.[53] We based our criteria on published guidelines acknowledging inevitable subjectivity of the assessment.[40,69] We assigned a medium or high risk of bias in the body of evidence when at least one individual RCT had a medium or high risk of bias, respectively. We defined treatment effect estimates as precise when pooled estimates had narrow 95 % CIs or the pooled sample had >300 events (using 25 % relative effect difference for calculation of optimal information size).[70] We did not quantify publication biases or selective outcome reporting biases because of the questionable statistical validity of the available tests.[71]

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 and to low if two or more criteria were not met. We defined evidence as insufficient if treatment effects or associations were examined by no studies or by a single study with unclear or high risk of bias.[53] We applied this approach regardless of the statistical significance of the results.

Assessing Applicability. We estimated applicability of the population by evaluating baseline subject characteristics in observational studies and clinical trials.[67] We reviewed the drugs applicable to practice in the US and patient-centered outcomes most valued by patients.

RESULTS

Of 5,244 identified references, we included 215 publications of RCTs (Figure 1) and 76 publications of non-randomized studies. Randomized trials examined 59 drugs from 14 classes (online Appendix Table 4). Most trials were funded by industry but did not disclose conflict of interest by study investigators. More than half of the RCTs had a medium risk of bias (online Appendix Table 5). Most RCTs (86 %) were double blind with unclear adequacy of allocation concealment or randomization.

The results were applicable to the target population. Most RCTs were conducted in the US and Western countries, used the International Headache Society's definition, and enrolled mostly middle-age women with episodic migraine (online Appendix Table 6). RCTs enrolled on average 210 adults, measured outcomes at 2 to 3 months follow-up, and reported about 15 % attrition.

Enrolled patients were mostly overweight and had an average of five monthly migraine attacks with or without aura. Almost half of enrolled subjects were naïve to migraine-preventive drugs. Patient age and baseline migraine characteristics did not statistically differ in most

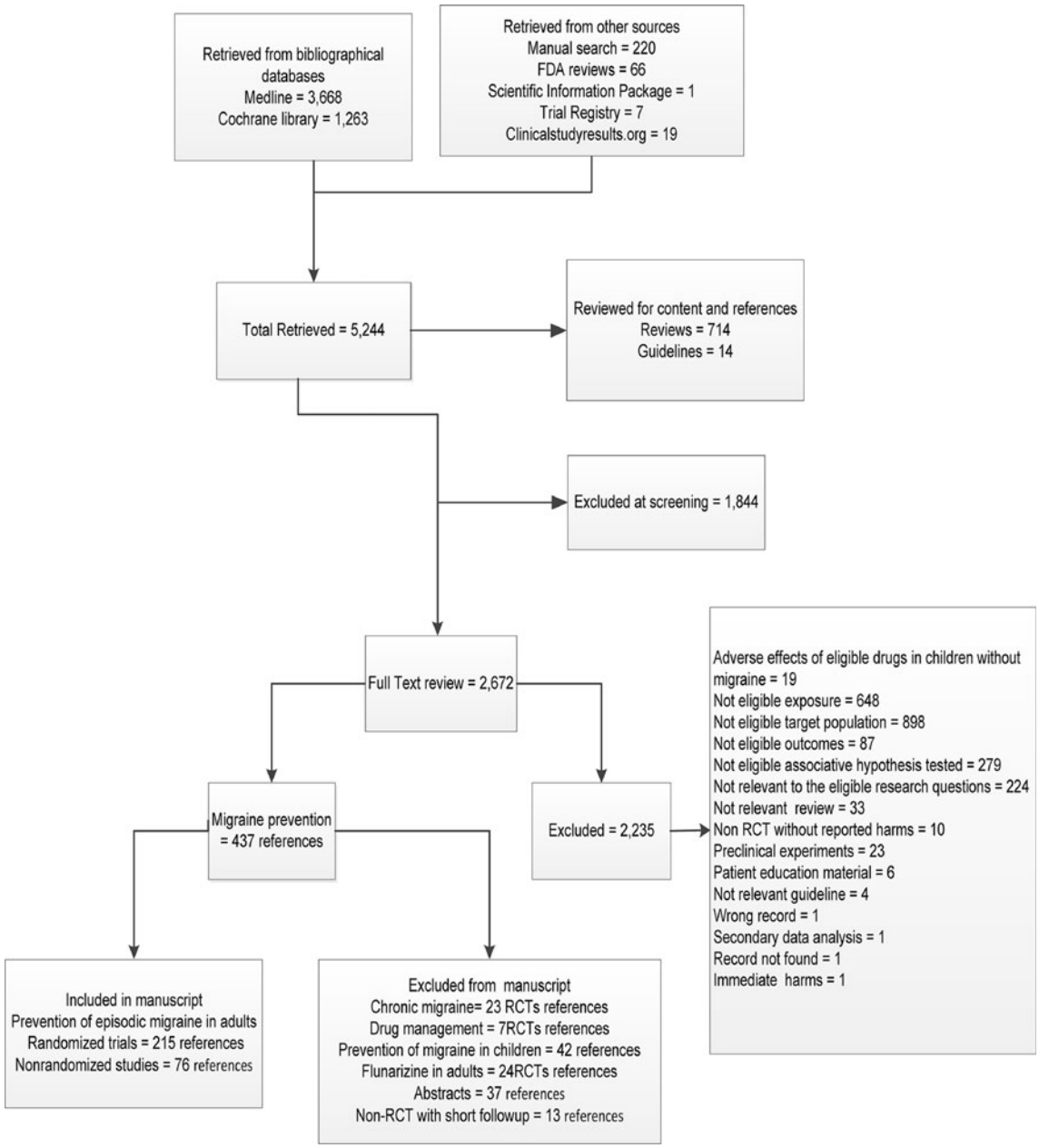

Figure 1. Study flow.

trials. Substantial variability in reporting comorbidities prevented us from using this information in quantitative synthesis of evidence. Most trials excluded patients with severe medical comorbidities or psychiatric illnesses, stroke, and vascular migraine. RCTs rarely reported patient characteristics that could modify drug effects (e.g. family history of migraine, ,socioeconomic status, or response to prior preventive treatments).

Most trials compared one active agent with placebo or another drug. RCTs rarely reported concomitant treatment details such as exact drugs and doses. However, most trials disallowed concomitant drugs during the run-in period and after randomization (implying no concomitant treatments were used in the RCTs). Strength of evidence was low because of medium or high risk of bias and imprecise estimates from individual or meta-analyzed RCTs.

Efficacy for Prevention of Episodic Migraine. All approved drugs were better than placebo in reducing monthly migraine frequency by ≥50 % in individual patients (clinical response) (Table 1 and online Appendix Table 7). Drugs would achieve a clinical response in 200 to 400 patients per 1,000 treated. We analyzed dose–response associations and found that an increase in target topiramate dose from 50 to 100 mg/day but not from 100 to 200 mg/day resulted in a higher response rate (≥50 % reduction in monthly migraine frequency).[72–74]

Approved drugs improved other patient-centered outcomes in addition to monthly migraine frequency. Topiramate improved quality of life measured by scores on the Headache Impact Test,[75] Migraine-Specific Questionnaire,[76] and Migraine Disability Assessment.[77] Topiramate improved general health status in a previously published pooled analysis of individual patient data from RCTs.[78] Divalproex in a larger dose of 1,500 mg/day increased the likelihood of a >50 % improvement in whether migraine attacks impaired usual activities or necessitated symptomatic medication and in reducing migraine attacks with nausea, vomiting, phonophobia, or photophobia.[79] Topiramate[73,74,80–82] and propranolol decreased use of drugs for acute migraine attacks.[83]

Among off-label drugs, pooled analyses offered low-strength evidence that the beta-blocker metoprolol (approved for migraine prevention in Europe) and calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by ≥50 % (Table 2). Antiepileptic gabapentin demonstrated some benefits; however, the validity of the results from one trial was questioned because of exclusion of patients from the analyses and biased tolerability conclusions.[84]

Individual RCTs demonstrated that three off-label beta blockers—acebutolol[85] (256 attributable events per 1,000 treated, 95 % CI, 105 to 407), atenolol[86] (333 attributable events per 1,000 treated, 95 % CI, 140 to 527), and nadolol[87] (250 attributable events per 1,000 treated, 95 % CI, 22 to 478)—were better than placebo in reducing monthly migraine attacks by ≥50 %.

Results from individual RCTs of angiotensin inhibiting drugs (angiotensin-converting enzyme [ACE] inhibitors and angiotensin II receptor blockers [ARB]) demonstrated effective migraine prevention. The ACE inhibitor captopril resulted in complete cessation of migraine (online Appendix Table 8), improved headache index scores by ≥50 %, and reduced depression symptoms in adults with comorbid hypertension and depressive symptoms for whom previous preventive antimigraine drugs had been ineffective.[88] The ACE inhibitor lisinopril[89] (233 attributable events per 1,000 treated, 95 % CI, 124 to 343) and the ARB candesartan[90] (350 attributable events per 1,000 treated, 95 % CI, 219 to 481) were better than placebo in reducing monthly migraine attacks by ≥50 %. Lisinopril was better than placebo in reducing pain measured with the Short Form 36 (SF-36) questionnaire, but did not decrease use of drugs for acute migraine attacks.[89] Candesartan decreased migraine-related disability, but had no effect on use of drugs for acute migraine attacks.[90] In contrast, the ARB telmisartan was not better than placebo in reducing monthly migraine attacks by ≥50 %.[91]

Comparative Effectiveness of Drugs for Prevention of Episodic Migraine. Pooled *direct* analyses demonstrated better effectiveness of propranolol over nifedipine and no differences between propranolol versus timolol or versus metoprolol and metoprolol versus aspirin (online Appendix Table 9). *Indirect* adjusted frequentist analyses demonstrated no differences among approved drugs in reducing monthly headache frequency by ≥50 % (online Appendix Table 10). Indirect adjusted frequentist analyses offered low-strength evidence that off-label ARB candesartan[90] resulted in greater odds of clinical response than approved drugs (online Appendix Table 10). Exploratory network Bayesian meta-analyses demonstrated effectiveness of all *approved drugs* with no differences between them (Figure 2 and online Appendix Table 11). Among *off-label drug classes*, angiotensin-inhibiting drugs (ACE inhibitors and ARBs) were more effective in reducing monthly migraine by ≥50 % when compared with antidepressants (OR, 2.8; 95 % CI, 1–7.5), off-label antiepileptics (OR, 2.7 95 % CI, 1–7.5), and ergot alkaloids (OR, 3.9; 95 % CI, 1.2 -14) (online Appendix Table 11).

Adverse Effects with Drugs for Prevention of Episodic Migraine. We identified 159 RCTs reporting adverse effects in 18,134 adults and focused on treatment discontinuation because of any adverse effects reported in 68 RCTs.

Topiramate in target doses of 100 and 200 mg/day (but not 50 mg/day) resulted in treatment discontinuation because of adverse effects more often than placebo (Table 3 and online Appendix Table 12). Compared with placebo, topiramate more often resulted in bothersome taste perversion, paresthesia, and fatigue leading to withdrawal (online Appendix Table 13). Taste perversion, weight loss, and paresthesia were the most common adverse effects (online Appendix Table 14). Larger target doses of topiramate caused higher risk of dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss[92] and led to treatment withdrawal due to higher risk of anorexia, depression, paresthesia, and impaired memory.[92]

Propranolol caused bothersome adverse effects leading to treatment discontinuation more often than placebo (Table 3). Among specific adverse effects, propranolol increased risk of diarrhea and nausea (online Appendix Table 15). Timolol increased risk of any adverse effects but not harms leading to treatment discontinuation.

Among off-label drugs, pooled direct analyses demonstrated that the antidepressant amitriptyline caused bothersome adverse effects leading to treatment discontinuation more often than placebo (Table 3).

Indirect adjusted frequentist analyses demonstrated no differences in treatment discontinuation due to adverse effects with approved drugs or approved versus off-label drugs. Exploratory Bayesian network meta-analy-

Table 1. Migraine Prevention with *Approved* Pharmacologic Preventive Treatments vs. Placebo in Adults, Results from Randomized Controlled Clinical Trials (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
Antiepileptics												
Divalproex >50 % reduction on migraine frequency	**Pooled**[79,115,116]	**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**	**Imprecise**	**Low**
	P value			**0.12**	**0.10**							
	I squared			**0.52**	**0.57**							
Topiramate on >50 % reduction on migraine frequency	**Pooled**[72,82,95,117–120]	**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**	**Precise**	**Moderate**
	P value			**0.04**	**<0.01**							
	I squared			**0.56**	**0.74**							
Topiramate on >50 % reduction on migraine days	**Pooled**[77,82,121]	**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**	**Imprecise**	**Moderate**
	P value			**0.01**	**0.04**							
	I squared			**0.77**	**0.68**							
Topiramate on ≥75 % reduction in migraine days	Pooled[82,121]	1086	22.3 [11.0]	1.9 (1.1 to 3.1)	0.10 (−0.01 to 0.20)			Low	Yes	Yes	Imprecise	Moderate
	P value			0.12	0.03							
	I squared			0.58	0.80							
Beta-blockers												
Propranolol >50 % reduction on migraine frequency	**Pooled**[122–125]	**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**	**Imprecise**	**Low**
	P value			**1.00**	**0.94**							
	I squared			**0**	**0**							
Timolol ≥50 % reduction in migraine frequency	**Pooled**[122,125,126]	**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**	**Imprecise**	**Low**
	P value			**0.73**	**0.61**							
	I squared			**0**	**0**							

Bold Significant differences when 95% CIs of absolute risk difference do not include 0

Table 2. Migraine Prevention with *Off-label* Pharmacologic Preventive Treatments vs. Placebo in Adults (the Results from Individual or Pooled with Random Effects Model 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
ACE inhibitors												
Lisinopril	Individual RCT[89]	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
Angiotensin II receptor blockers												
Candesartan	Individual RCT[90]	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
Telmisartan	Individual RCT	95	33[23]	1.4 (0.7 to 2.7)	0.1 (−0.1 to 0.3)			High	Yes	NA	Imprecise	Low
Antiepileptics												
Gabapentin	**Pooled[127–129]**	**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**	**Imprecise**	**Low**
	P value			**0.49**	**0.85**							
	I squared			**0**	**0**							
Beta-blockers												
Metoprolol	**Pooled[130–133]**	**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**	**Imprecise**	**Low**
	P value			**0.42**	**0.39**							
	I squared			**0**	**0**							
Magnesium												
Magnesium	Pooled[134,135]	137	33.8 [25.8]	1.3 (0.7 to 2.3)	0.08 (-0.09 to 0.26)			Low	Yes	No	Imprecise	Low
	P value			0.27	0.25							
	I squared			0.19	0.25							
Selective calcium channel blockers												
Nimodipine	**Pooled[130,131]**	**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**	**Imprecise**	**Low**
	P value			**0.13**	**0.19**							
	I squared			**0.58**	**0.41**							

Bold Significant differences when 95% CIs of absolute risk difference do not include 0

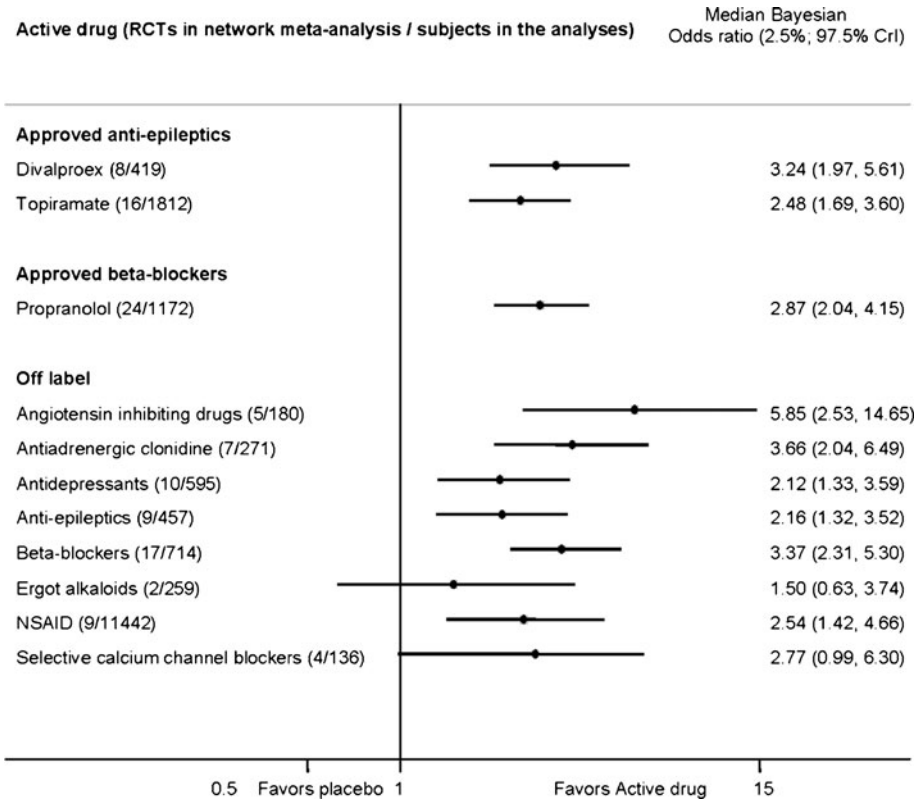

Figure 2. Bayesian network meta-analysis of clinical response to drugs vs. placebo (66 RCTs of 14,774 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults. *CrI* Credible intervals. Clinical response was defined as 50 % or more reduction in monthly migraine attacks or perceived clinically important treatment success. We used a heterogeneous random effects model that assumes correlation within a study (rho=0.5) and heterogeneity between studies. *NSAID* Nonsteroidal antiinflammatory drugs.

ses demonstrated that topiramate and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo (Figure 3). According to network meta-analysis, off-label beta-blockers were the least likely to result in adverse effects leading to treatment discontinuation in adults with episodic migraine. Subjects did not experience increased risk of adverse effects that would lead to treatment discontinuation with off-label angiotensin-inhibiting drugs (online Appendix Table 16).

Nonrandomized studies with high risk of bias suggested that 10 to 20 % of patients discontinued antiepileptic drug treatments at 1 year or longer of follow-up.

Drug Effect Modification by Select Patient Characteristics. Evidence was limited to individual RCTs examining drug effect modification by select patient characteristics. Amitriptyline was better than placebo in reducing monthly migraine, but only in patients with depression or baseline frequent and severe migraine[93] (OR, 2.4; 95 % CI, 1.45-3.8 for every additional day of migraine at baseline).[94] No trials directly compared drug effects in patients with and without aura. Several *post hoc* subgroup analyses of topiramate versus placebo provided inconsistent efficacy evidence regarding aura.[95,96]

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). Drugs demonstrated similarly moderate relative effect size: drugs prevented half or more migraine attacks in 200 to 400 patients per 1,000 treated.

Critical assessment of the available evidence suggested that strength of evidence was moderate only for topiramate and low for other drugs because of risk of bias and imprecise estimates. We found it difficult to evaluate the role of financial conflict of interest and industry participation in data analyses because many studies were conducted prior to mandatory requirements for financial disclosure, leading to inconsistent reporting and insufficient detail from individual studies.[97] Studies inconsistently reported subjects' baseline severity, comorbidities, and concomitant treatments[2,98] as well as family history of migraine, socioeconomic status, or response to prior

Table 3. 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 [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 strength of evidence
Compared with placebo							
Approved antiepileptics							
Divalproex[115,116]	346	9.8 [7.8]	1.2 (0.5 to 2.7)	0.02 (−0.05 to 0.10)			Low (medium ROB, imprecise, inconsistent)
Topiramate[21,80,81,95,118,120,136,137]	**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)**
Approved beta-blockers							
Propranolol[124,138]	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)**
Off-label ACE inhibitors							
Lisinopril[89]	120	3.3 [1.7]	2.0 (0.2 to 21.5)	0.02(−0.04 to 0.07)			Low (imprecise, individual RCT)
Off-label angiotensin II receptor blockers							
Telmisartan[91]	95	2.1 [2.1]	1.0 (0.1 to 15.2)	0.00(−0.06 to 0.06)			Low (imprecision, individual RCT)
Off-label antiadrenergics							
Clonidine[139,140]	334	2.4 [0.6]	2.8 (0.4 to 18.5)	0.02 (−0.01 to 0.05)			Low (medium ROB, imprecise)
Off-label antidepressants							
Amitriptyline[93,141]	**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[142,143]	124	11.7 [6.3]	1.9 (0.6 to 6.1)	0.05 (−0.05 to 0.15)			Low (medium ROB, imprecise)
Off-label antiepileptics							
Gabapentin[127–129]	270	17.0 [7.7]	1.9 (0.9 to 4.2)	0.07 (−0.01 to 0.15)			Low (medium ROB, imprecise)
Lamotrigine[120,144]	178	12.8 [6.0]	2.4 (0.5 to 12.2)	0.14 (−0.17 to 0.44)			Low (imprecise, inconsistent)
Valproate[145,146]	150	6.7 [5.3]	1.3 (0.3 to 4.9)	0.01 (−0.07 to 0.08)			Low (medium ROB, imprecise)
Off-label magnesium							
Magnesium[134,135]	150	7.7 [1.4]	3.8 (0.7 to 22.4)	0.06 (0.00 to 0.13)			Low (Imprecise, inconsistent)
Off-label nonsteroidal antiinflammatory drugs							
Naproxen[147,148]	172	3.5 [1.2]	2.3 (0.3 to 15.4)	0.02 (−0.03 to 0.07)			Low (high ROB, imprecise, inconsistent)
Off-label selective calcium channel blockers							
Nimodipine[130,149]	155	3.9 [6.3]	0.7 (0.2 to 2.6)	−0.03 (−0.09 to 0.04)			Low (medium ROB, imprecise, inconsistent)
Compared with active treatment: approved antiepileptic vs. off-label antidepressant							
Topiramate vs. amitriptyline[150,151]	399	18.3 [21.3]	0.9 (0.6 to 1.3)	−0.04 (−0.11 to 0.04)			Low (medium ROB, imprecise)

SOE Strength of evidence, ROB risk of bias. 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

preventive treatments.[99,100] Few studies provided evidence for individualized treatment decisions with clear descriptions of planned stratified randomization and subgroup analyses.[101] No trials examined the role of genetic polymorphism in drug metabolism and effects.[102–104] Migraine prevention trials did not address teratogenic effects,[105] anorgasmia,[106] impotence,[107] and other harms of antiepileptic drugs that can deter long-term adherence to preventive drugs.

Informed clinical decisions should balance the benefits and harms attributable to specific drugs.[108] The most recent guidelines from the American Academy of Neurology and the American Headache Society recommend the four FDA-approved drugs—topiramate, divalproex, propranolol, and timolol—for adult migraine prevention.[109] These guidelines focused on published evidence only and differed in recommending off-label drugs, including beta-blockers and angiotensin-inhibiting drugs. Further, current guidelines do not include consideration of the balance between benefits and harms of drugs as a basis for clinical decision-making.[110]

Our report has limitations. We did not contact authors for details about unreported benefits and harms or about methodological quality in cases of poor reporting of risk of bias criteria; the cost-effectiveness of this pursuit is still being debated.[111,112] We justify using indirect network meta-analyses since trials did not differ by reported baseline subject characteristics. However, indirect comparisons did not address unreported baseline differences in comorbidities or socioeconomic status. We

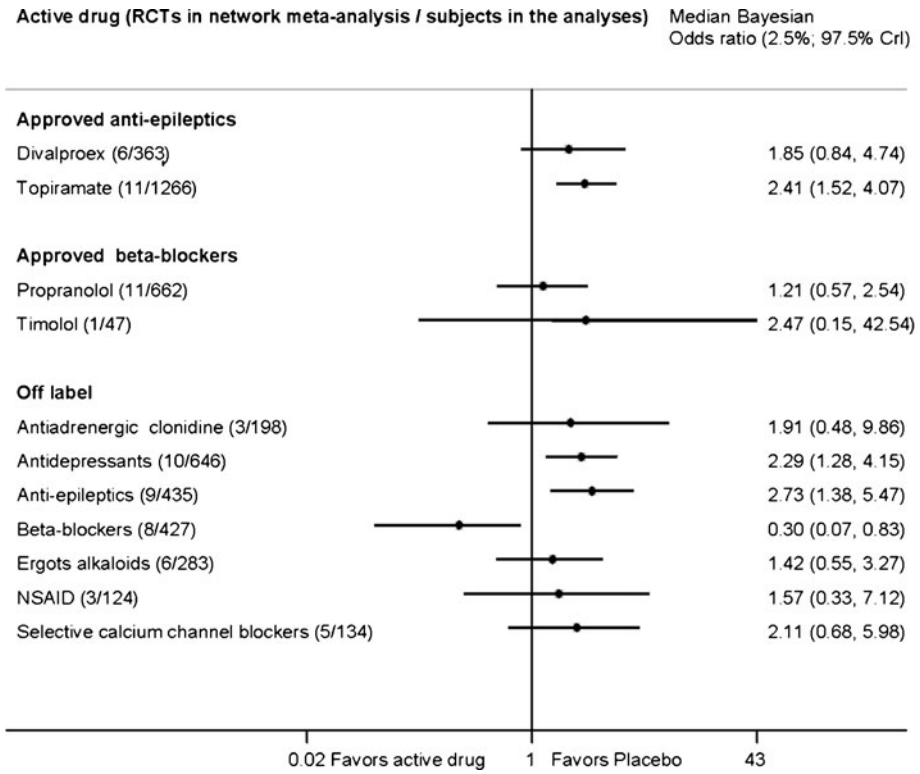

Figure 3. Bayesian network meta-analysis of treatment discontinuation due to intolerable adverse effects with drugs vs. placebo (47 RCTs of 3,054 adults) in randomized controlled clinical trials that aimed to prevent migraine in adults. *CrI* Credible intervals. We used a heterogeneous random effects model that assumes correlation within a study (rho=0.5) and heterogeneity between studies. RCTs of angiotensin-inhibiting drugs do not report intolerable adverse effects. *NSAID* Nonsteroidal antiinflammatory drugs.

did not use tests with questionable statistical validity to quantify publication bias; instead, we identified low publication rates of NIH-funded grants and registered studies of migraine prevention. Available data did not allow us to determine exact reasons for low availability of results. Complete information about all conducted studies may change our low strength of evidence conclusions in the future. Although judgments in ranking strength of evidence were subjective,[40] our transparent appraisal provides useful information for informed decision-making in practice and future research needs.

Future well-designed RCTs should examine the comparative effectiveness of the approved and the most effective off-label drugs by patient demographics, migraine family history, comorbidities, and response to prior treatments. Analyses of administrative databases should examine emergency room visits for treatment of migraines among adults taking approved and off-label preventive drugs.[17] Prospective pharmacovigilance methods[113,114] should be used for routine monitoring of off-label drug use and associated adverse effects with migraine preventive drugs.

Based on our comprehensive network analysis of comparative effectiveness and harms with migraine preventive drugs in adults, we conclude that approved drugs and off-label angiotensin-inhibiting drugs (lisinopril, captopril, and candesartan) or off-label beta-blockers (metoprolol, acebutolol, atenolol, and nadolol) were effective in preventing episodic migraine in adults. Exploratory network meta-analyses of all available evidence suggested that off-label angiotensin-inhibiting drugs demonstrated the most favorable benefit to harm ratio.

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