



Effective Health Care Program

Future Research Needs Paper
Number 35

Preventive Pharmacological Treatments for Migraine in Adults: Future Research Needs



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Number 35

Preventive Pharmacological Treatments for Migraine in Adults: Future Research Needs

**Identification of Future Research Needs From Comparative Effectiveness Review
No. 103**

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Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of evidence reports and technology assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The reports and assessments provide organizations with comprehensive, science-based information on common, costly medical conditions and new health care technologies and strategies. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

An important part of evidence reports is to not only synthesize the evidence, but also to identify the gaps in evidence that limited the ability to answer the systematic review questions. AHRQ supports EPCs to work with various stakeholders to identify and prioritize the future research that is needed by decisionmakers. This information is provided for researchers and funders of research in these Future Research Needs papers. These papers are made available for public comment and use and may be revised.

AHRQ expects that the EPC evidence reports and technology assessments will inform individual health plans, providers, and purchasers as well as the health care system as a whole by providing important information to help improve health care quality. The evidence reports undergo public comment prior to their release as a final report.

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

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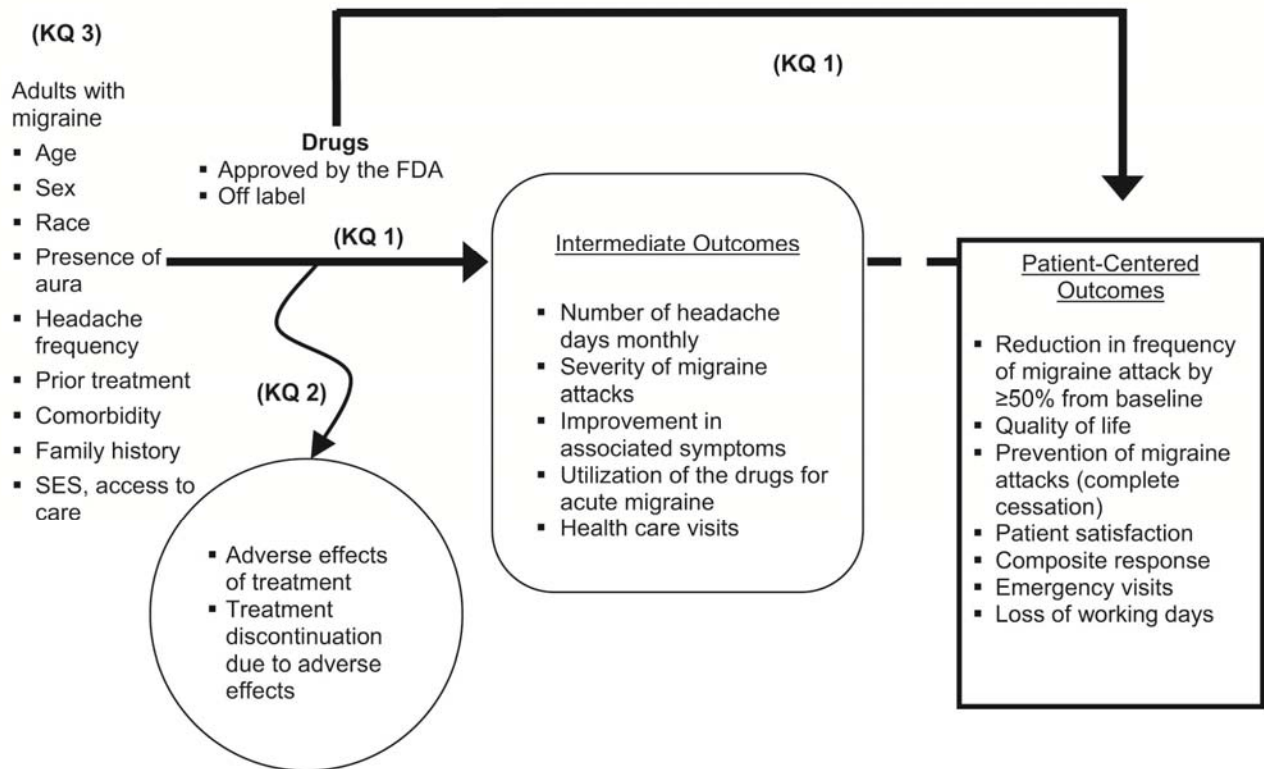
Executive Summary

Background

This Future Research Needs (FRN) project is a followup to the Comparative Effectiveness Review (CER), “Preventive Pharmacologic Treatments for Migraine.”¹ The review was motivated by uncertainty around the effectiveness, comparative effectiveness, and safety of pharmacologic treatments for the prevention of episodic or chronic migraine in adults. To identify research needs, this FRN project used a deliberative process to identify evidence gaps, translate gaps into researchable questions, and solicit stakeholder opinion on the importance of research questions. Addressing these research needs should provide information potentially of value to decisionmakers.

The research questions addressed in the CER relied upon an analytic framework from the original CER (Figure A). The framework describes a process experienced by adults with episodic or chronic migraine seeking preventative pharmacologic treatments. Differentiating between chronic or episodic migraine according to their clinical definitions depends on headache frequency, frequency of migraine type headaches, the presence of aura, and the possibility of headaches associated with overusing acute pain medication. However, in practice, these categories are often simplified in studies with episodic indicating fewer than 15 headache days per month and chronic indicating 15 or more headache days per month). The review addressed important Key Questions (KQs) about the efficacy and comparative effectiveness of these treatments (KQ 1); evaluating the safety of these treatments (KQ 2); and the identification of patient characteristics that predict the effectiveness and safety of pharmacologic treatments for preventing migraine attacks in adults (KQ 3).

Figure A. Analytic framework



KQ = Key Question; SES = socioeconomic status

Note: 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?

Findings of CER

The CER synthesized data from eligible randomized controlled trials (RCTs) for efficacy and comparative effectiveness.¹ Data from these RCTs and additional eligible nonrandomized studies was synthesized for harms. Key findings are summarized below.

Prevention of Chronic Migraine

Efficacy

Only one drug for chronic migraine, onabotulinumtoxinA, was examined in more than one RCT. OnabotulinumtoxinA was better than placebo in reducing monthly migraine attack by 50 percent or more. A single RCT reported that topiramate was better than placebo in achieving a reduction of headache frequency, but not better than placebo in reducing monthly migraine attacks 50 percent or more.

Comparative Effectiveness

Five individual RCTs provided low-strength evidence about the comparative effectiveness of onabotulinumtoxinA versus other drugs for chronic migraine prevention. Individual RCTs examined the comparative effectiveness of onabotulinumtoxinA 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 onabotulinumtoxinA; however, need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of onabotulinumtoxinA versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life. A single RCT reported that propranolol added to topiramate did not effectively prevent chronic migraine in patients for whom topiramate monotherapy had failed.

Safety

OnabotulinumtoxinA resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo. Increase in risk of adverse effects was dose responsive.

Individual RCTs demonstrated less frequent treatment discontinuation due to adverse effects with onabotulinumtoxinA than topiramate or amitriptyline.

Prevention of Episodic Migraine

Efficacy

All approved drugs (propranolol, timolol, topiramate, and divalproex sodium) were better than placebo in reducing monthly migraine frequency by 50 percent or more in individual patients. Rates of clinical response were moderate, 200 to 400 patients per 1,000 treated. In addition to ≥ 50 percent reduction in monthly migraine frequency, individual RCTs of approved antiepileptic drugs and beta blockers improved other patient-centered outcomes. Topiramate demonstrated significant improvements for general health status, quality of life, and disability, with score improvements on the Medical Outcome Study Short Form 36 (SF-36) of more than 200 percent for self-reported vitality and more than 100 percent for improvement in pain and general health. Divalproex in a larger dose of 1,500 mg/day increased the likelihood of a 50 percent improvement in whether migraine attacks impaired usual activities or necessitated symptomatic medication and in reducing migraine attacks with nausea, vomiting, phonophobia, or photophobia. Topiramate and propranolol decreased use of drugs for acute migraine attacks.

Among off-label drugs, pooled analyses demonstrated that antiepileptic gabapentin, beta-blocker metoprolol, and calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by 50 percent or more.

Individual RCTs demonstrated that the off-label anti-epileptics carbamazepin and valproate (but not acetazolamide, lamotrigine, or oxcarbazepine) were better than placebo in reducing monthly migraine attacks by 50 percent or more. Individual RCTs demonstrated that off-label beta blockers acebutolol atenolol and nadolol (but not pindolol or alprenolol) were better than placebo in reducing monthly migraine attacks by 50 percent or more.

Individual RCTs of off-label angiotensin converting enzyme (ACE) inhibiting drugs demonstrated promising results. The ACE 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, improvement in Headache Index scores by 50 percent or more, and reduced 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 off-label angiotensin II antagonist (ARB) candesartan was better than placebo in achieving a clinical response defined as a 50 percent or more reduction in migraine days. Candesartan also decreased migraine-related disability but had no effect on use of drugs for acute migraine attacks. In contrast, ARB telmisartan was not better than placebo in reducing monthly migraine attacks by 50 percent or more.

Comparative Effectiveness

Pooled analysis was possible for only four paired drug comparisons for the prevention of episodic migraine, and this analysis demonstrated few significant differences between individual drugs. Exploratory Bayesian network meta-analysis and indirect adjusted analysis of such drugs found no differences among approved drugs. Approved drugs were more effective than off-label drugs except for the angiotensin II receptor blocker candesartan, which was more effective than topiramate, divalproex, and propranolol. Exploratory Bayesian network meta-analysis demonstrated that the approved drugs topiramate, divalproex, and propranolol, and off-label drug classes including angiotensin inhibiting drugs were better than placebo. The strength of the association was the largest with angiotensin inhibiting drugs.

Safety

Bothersome adverse effects leading to treatment discontinuation were greater than placebo for topiramate in doses of 100 and 200 mg/day (but not 50 mg/day) and propranolol.

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.

In direct comparisons of divalproex or valproate versus placebo, treatment discontinuation due to adverse effects did not differ. Pooled analysis showed no differences in treatment discontinuation with topiramate versus amitriptyline.

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. A network meta-analysis indicated that off-label ACE inhibitors and beta-blockers were the safest treatment option for adults with episodic migraine.

Patient Characteristics

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 depression or with baseline frequent and severe migraine.

- Topiramate was more likely to reduce migraine attacks in women but not in men according to one low-risk-of-bias RCT.
- Several post hoc subgroup analyses of topiramate versus placebo provided inconsistent evidence of the drug efficacy in respect to aura.

Evidence Gaps

The CER identified gaps and biases in available evidence and made future research recommendations.¹ Findings from the CER drew conclusions about the efficacy and comparative effectiveness of the off-label use of ACE inhibitors and ARBs for migraine prevention that were stronger than current guidelines suggest. Because these conclusions were drawn from a small number of RCTs, future research could refute or validate the results of these early studies. Additionally, well-designed randomized clinical trials should examine the comparative effectiveness via head-to-head trials of approved drugs and the most effective off-label ACE inhibitors, ARBs, antidepressants, and 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. The long-term efficacy of most preventive pharmacologic treatments is unknown; evidence on improving quality of life was inconsistent across individual drugs; future research could help clarify these issues. Investigators should strive to better capture adverse effects associated with migraine preventive drugs. Additionally, future research synthesis would benefit from trial registration and posting of results on www.ClinicalTrials.gov.

Project Purpose

Our FRN project identifies and prioritizes research needs arising from the status of current literature on efficacy, comparative effectiveness, and safety of preventative pharmacologic treatments in adults for the prevention of episodic or chronic migraine. These research needs are presented along with research design considerations and represent the opinion of a select group of stakeholders on issues on which future research has potential value to the current body of evidence.

Methods

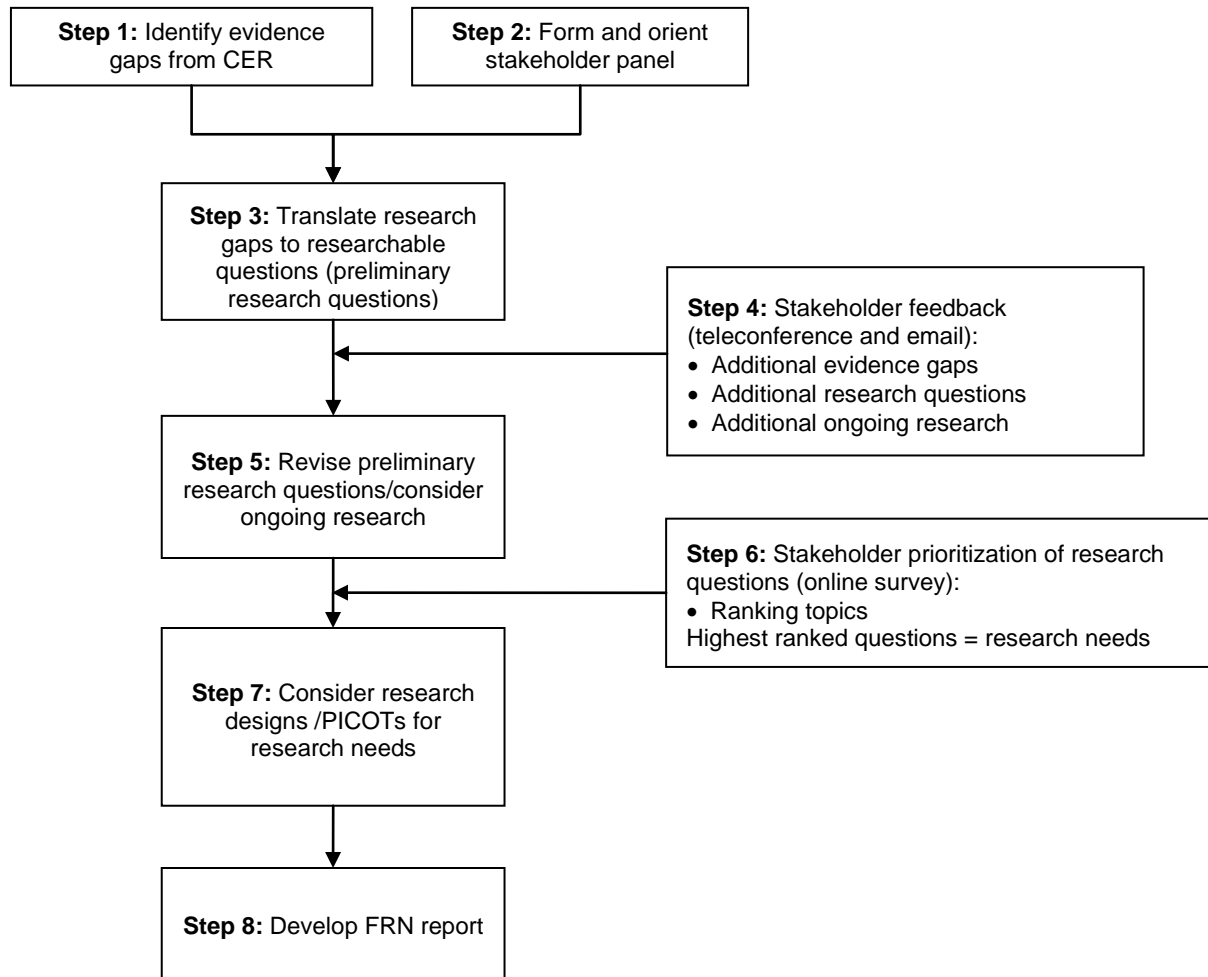
We used a deliberative process to identify and prioritize research questions relevant to the KQs addressed in the CER. Figure B illustrates the eight steps used to accomplish the objectives of this project.

First, we translated the research gaps identified in the CER into research questions. Second, we assembled a diverse stakeholder panel with representation from various perspectives relevant to the topic. Invited research representatives were national experts who were familiar with: (1) evidence-based medicine; (2) the obstacles often associated with conducting well-designed research on migraine prevention; and (3) preventive pharmacologic interventions from the fields of neurology, headache medicine, and pharmacy. We invited participation from representatives from organizations supporting or conducting relevant research, including the representatives from organizations supporting or conducting relevant research including the National Institute of Neurological Disorders and Stroke (NINDS), the National Headache Foundation, and others. Finally, we engaged providers and consumers, because the decisional dilemmas faced by these groups are critical to identifying and prioritizing research questions.

We first held conference calls with stakeholders to refine the draft research questions. Based upon these conversations and an assessment of recent and ongoing work, we revised our initial list of research questions. This revision included separating the questions into categories (methodological research questions that need to be addressed to enhance the usefulness of current research and topical research questions that have not been sufficiently addressed in the current literature, separated further into those addressing episodic migraine and those addressing chronic migraine). We sent this list of research questions to stakeholders for prioritization. Stakeholders assigned a total of seven “stars” (up to three stars for one question) to methodological research questions and a total of seven stars (up to three stars for one question) for topical episodic and chronic research questions from a total of 21.

Cumulative stars across all stakeholders were used to rank order each category of research questions to determine their relative importance. Based upon natural breakpoints in the rankings, we determined high, moderate, and low-priority research questions. High-priority questions were deemed research needs. We then identified and discussed research design considerations for those identified research needs.

Figure B. Project flow



CER = Comparative Effectiveness Review; FRN = Future Research Needs; PICOTS = Population, intervention, comparison, outcome, timing, setting

Results

Prioritization Results

We analyzed stakeholder prioritization results. Of the 10 stakeholders invited to rank research questions, 6 ranked methodological questions, 7 ranked topical questions related to episodic migraine, and 6 ranked topical questions related to chronic migraine.

Methodological Research Needs

Three of the eight methodological research questions received five or more stars from four to five stakeholders, delineating the top three research questions according to our stakeholders. We designated this top tier our methodological research needs:

- How should research of pharmacologic treatment for chronic migraine define treatment success?
- How should chronic migraine populations be defined in trials?
- What biomarkers help predict treatment response?

Considerations for Potential Research

These methodological research needs could be addressed through consensus development, additional systematic reviews, post hoc analyses of previous trial data, and/or qualitative research. One way to identify outcomes that are specifically valued by chronic migraine patients may be to build on the work of the Common Data Elements (CDE) Headache Preventive Therapies group.² Although this group focused on selecting measures for headache in general, the knowledge they gained would likely offer direction for identifying measures specific to migraine.

Reviewing the literature for reports of patient opinions or preferences would provide background, and qualitative research might also contribute. For example, by using focus groups with patients with chronic migraine and their families, employers would help to identify patient-centered outcomes. Preferred outcomes are likely associated with current condition severity and treatment burden.

The task of arriving at a consensus definition of chronic migraine that is easily implemented in trials and translates well to clinical practice has proven challenging. However, such a definition should be achievable with continued consultations among researchers and providers along with continued field testing of various definitions.³

Decisionmakers would be greatly assisted by further efforts to synthesize knowledge of biomarkers that can be reliably used to assist in predictions of preventive pharmacologic treatment response. Although research does continue to identify these markers, synthesizing the current knowledge on this topic could help to identify specific directions to next approach. Knowledge could also be gained through post hoc analysis of previous trial data to explore potential relationships between specific biomarkers and patient outcomes.

Topical Research Needs

Natural breakpoints in weighted rankings revealed six prominent topical research needs relevant to episodic migraine and three relevant to chronic migraine. Topical research needs addressed a range of PICOTS elements including the population, intervention, outcome, and

timing. Stakeholders did not prioritize basic efficacy questions that have been studied in numerous trials. Nor did they prioritize questions about the comparative effectiveness of different treatments. They were most interested in identifying specific details about these efficacious treatments that can better inform practice decisions and communication with patients. Although most of these research needs were directly addressed by the CER, two research needs were tangential to the CER KQs. Those addressed by the CER remain research needs because the evidence on these specific questions was insufficient or lacked strength.

Episodic Migraine: First Topical Research Need

- What is the optimal duration of preventive pharmacologic treatments for episodic migraine?

The CER addressed this research need with a question examining the influence of dose and duration of treatment on patient-centered outcomes (KQ 1e). The studies identified for this KQ examined different doses of the drugs and measured outcomes at 2 to 3 months of followup. The short timeframes analyzed in trials along with some guidance suggesting that successful preventive drugs be taken for “3 to 6 months” or for “several months”⁴ seem to contradict the nature of the condition and the length of treatment that occurs in practice. Limited research exists regarding migraine frequency after discontinuation of preventive treatment.⁵ The CER did not find good evidence for long-term effectiveness and safety with preventive drugs.

The recent guideline report from the Canadian Headache Society addressed the question of how long to continue preventive treatment, concluding that little evidence is available to inform these decisions. They recommended that tapering and discontinuing preventive medications be considered after 6 to 12 months of successful treatment.⁴ Stakeholders agreed that the ideal time to treat patients with preventive pharmacologic treatments it is not well understood. Future studies testing these longer timeframes for discontinuing preventive pharmacologic treatment would inform clinical practice.

Research Design Considerations

Studies of the efficacy or comparative effectiveness of preventive pharmacologic treatments for migraine need to use experimental designs to achieve valid results. These studies will likely test a hypothesis that longer durations of preventive treatment are more effective than shorter durations. Therefore, studies should include groups of patients with variation in treatment duration in order to test the hypothesis by identifying differences in outcomes between groups. These treatment-related research questions are most appropriately studied with adequately powered double-blind randomized controlled trials. Double blinding is critical for several reasons. First, the nature of the condition relies on patient report and provider judgment for diagnosis and therefore inclusion in intervention studies, as opposed to conditions that use definitive lab values for diagnosis. Second, outcomes used to measure effectiveness are also subjective and self-reported. The large placebo response observed in studies on this topic creates another strong indication that blinding is essential to the validity of studies on this topic.

In addition to blinding, an RCT designed to identify the optimal duration of preventive pharmacologic treatment should pay particular attention to subgroups. Optimal duration of treatment likely varies according to certain patient and migraine characteristics. Therefore, these subgroups need to be identified when the RCT is planned and power calculations should be conducted to insure adequate subgroup sample sizes.

Episodic Migraine: Second Topical Research Need

- If preventive pharmacologic treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels?

This research need was not specifically addressed within the KQs of the CER, but relates to treatment duration addressed in KQ 1e and the previous research need (Episodic Migraine: First Topical Research Need). A recent review discusses the few studies that have evaluated discontinuation after successful short courses of preventive drugs (topiramate, valproate, and flunarizine) and reports that relapse does occur in most patients.⁴ Stakeholders agreed that an improved understanding of the consequences of discontinuing treatment was needed.

Research Design Considerations

This question might be considered a subquestion to an RCT addressing the first research need regarding optimal duration of treatment. However, a more clinically meaningful population in which to analyze outcomes after discontinuing treatment would be those treated successfully with a preventive pharmacologic treatment for which treatment was discontinued treatment based on some objective clinical measure, as opposed to time frame alone.

An observational study design could be used to evaluate the effects of discontinuing preventive pharmacologic treatment in this population. Patients achieving success with treatment and ready to discontinue treatment could be recruited and followed over time, and their headache frequency could be assessed at multiple intervals. As with the previous research need, subgroups based upon patient or disease characteristics (i.e., length of time with episodic migraine, comorbidities) are likely important correlates of post treatment headache treatment and studies designed to test specific subgroups of patients will be most valuable.

Episodic Migraine: Third Topical Research Need

- What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine?

CER investigators identified several RCTs that examined quality of life, however judged that the evidence lacked the strength necessary for robust conclusions and merited future research. Specifically, few studies assessed the clinical importance of the changes in quality of life or disability scales. The CER does discuss results from several trials that analyzed quality of life types of outcomes (as measured with a variety of scales) and suggests that preventive treatment typically improved quality of life (topiramate, divalproex). While use of acute medications is a commonly used outcome in episodic migraine trials, other health care use outcomes such as emergency department visits were not often included.

Our stakeholders agreed that the currently available evidence does not adequately measure the true burden of preventative pharmacologic treatments for episodic migraine. For instance, a treatment that decreases headache frequency by 50 percent may not be perceived as an improvement if patients become so fatigued or nauseous that they are still unable participate in social roles and activities. Therefore, additional efficacy trials with outcomes measured using validated quality of life measures would provide a clearer indication of the true benefit of preventive medications. Future research is needed to address efficacy, comparative effectiveness, and safety in terms of the net impact on patients' lives.

Research Design Considerations

As we previously mentioned, migraine prevention efficacy is best studied with appropriately powered double-blind randomized controlled trials. Trials to address this research need will be similar to trials that have been previously conducted, but using additional patient-centered outcomes.

Episodic Migraine: Fourth Topical Research Need

- What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine?

Current clinical practice for migraine prevention often involves multimodal treatments (a combination of pharmacologic, psychological, lifestyle, cognitive, and other interventions). How well these combined treatments work, the marginal benefits above pharmacologic treatments alone, and in which patients they offer a greater benefit over pharmacologic treatments alone needs improved understanding. The four studies evaluating multimodal treatments analyzed in the CER suggested that these programs may offer benefits beyond preventive pharmacologic treatments alone. Stakeholders suggested the need for additional research to address these programs be conducted with precise intervention definitions or protocols, and assessments of how they work and with which patients.

Research Design Considerations

RCTs that assess the efficacy of these combined interventions would add value to the current body of evidence. Studies addressing this research need will test the hypothesis that multimodal treatments are superior to preventive pharmacologic treatments. The most important multimodal treatments to test are those commonly used in practice and are likely to include a preventive medication along with some type of behavioral therapy as compared with medication as the only preventive treatment. Therefore, the most important trials to address this research need are large comparative effectiveness trials with a diverse set of participants and sample sizes of subgroups of patients sufficient to test subgroup effects.

Episodic Migraine: Fifth Topical Research Need

- Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)

This research need addresses combinations of preventive medications, while the previous question addressed combinations of different types of treatments. Combinations of preventive pharmacologic treatments are used for episodic migraine in some circumstances. The CER does not draw conclusions about the efficacy or comparative effectiveness of drug combinations across classes for prevention of episodic migraine. However, combinations are often used in practice especially in patients with refractory migraine (failed treatment with one drug alone).⁴ Patients that cannot tolerate certain drugs at necessary dosage might better tolerate combination of drugs at lower doses. While evidence about combination preventive medication treatment is not available from blinded RCTs, several open label trials suggest that preventive drug combinations may be effective when treatment with a single drug has failed.⁴ Stakeholders are interested in an improved evidence base regarding polypharmacy for migraine prevention (i.e., what is the benefit of adding a second drug when patients are not effectively treated with one

drug? Are drug side effects lessened when two drugs are used at lower dosages instead of one drug at a higher dose?).

Research Design Considerations

RCTs that compare the effectiveness of multidrug combinations to single drug treatment are necessary to address this research need. The most important drug combinations to test are those commonly used in practice or those suggested in previously conducted open-label trials. The target population for such trials would be individuals who have failed treatment trials with several preventive medications. Again, blinding and sample size are key considerations. As with most of these research needs, subgroups will likely be a very important predictor of response and key subgroups relevant to this research question should be identified. Once identified, power calculations should be conducted to determine the necessary sample size to test differences between subgroups. Because subgroup analysis may be important and we are comparing two active treatments which may have a small marginal difference, the sample size necessary to address this research need will be large and therefore, resource requirements high.

Episodic Migraine: Sixth Topical Research Need

- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)

Disease characteristics among adults suffering from episodic migraine can vary widely. Patients may have suffered from episodic migraine for as little as a few months to several years providing a wide range of chronicity. In addition to chronicity, other disease characteristics vary as well. Some individuals may suffer from an average of five headaches per month and others 15. The duration and severity of those headaches can also vary widely from individual to individual. Many of these characteristics are thought to influence patient response to preventive pharmacologic treatment. KQ3 of the CER addressed the patient characteristics that influenced response to preventive medication. However, data was only available for a few condition-specific categories (e.g., migraine with aura, baseline migraine frequency) for certain medications. The Canadian Headache Society guidelines recommend preventive migraine medications specifically for patients with certain comorbidities (increased body mass index, hypertension, and depression/anxiety).⁴ Our stakeholders agreed that an improved understanding of how disease characteristics modify treatment effectiveness would aid decisionmaking.

Research Design Considerations

While post hoc analyses of previous RCTs or cohort studies could be used to identify potential relationships between specific disease characteristics and response to treatment with particular drugs, a large RCT is the best approach to testing the hypothesized relationship. Most valuable would be to test relationships previously identified, but rated insufficient or low strength evidence, as well as relationships suspected based on observational studies or clinical practice. Power calculations will be critical to determine sample size with adequate subgroup populations necessary to test differences between groups. If RCTs are not feasible, prospective cohort studies could be designed to enable larger samples, but investigators must take adequate steps to adjust for selection bias.

Chronic Migraine: First Topical Research Need

- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)

Fewer research questions rose to the top of the ranking process for chronic migraine prevention. While far fewer individuals suffer from chronic migraine than episodic migraine, the impact of the condition on their lives is substantially greater. Improved knowledge around these treatment-specific research needs could eventually lessen the disease burden among those suffering from chronic migraine.

This research need mirrors one aimed at the episodic migraine population. Enhanced knowledge on disease characteristics and response to treatment appears even more critical with regard to chronic than episodic migraine. However, data examining these relationships is even scarcer with regard to chronic migraine. The CER reported one trial that examined subgroup effects (prior topiramate use and medication overuse) of preventive treatment (topiramate vs. topiramate plus propranolol) in chronic migraine. Many other subgroups need to be analyzed to improve understanding of the influence of specific disease characteristics.

Research Design Considerations

Design issues for RCTs regarding preventive pharmacologic treatments for chronic migraine are essentially identical to those of episodic migraine for the corresponding research need, but have greater challenges. Conducting RCTs with chronic migraine populations will be more difficult given the lower prevalence of the condition. Multi-site trials should be considered to recruit adequate sample sizes. Additionally, investigators might expect a greater degree of attrition among chronic migraine participants than among episodic migraine participants due to their poorer health status.

Chronic Migraine: Second Topical Research Need

- What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)

While this research question was not highly prioritized for episodic migraine, it is much more relevant for chronic migraine because these individuals often need preventive medications for long periods of time. This specific question was not addressed by the CER; however, included trials had timelines much shorter than 1 year. If chronic migraine patients are expected to take preventive medications for years, we need an improved understanding of the long-term effectiveness and harms of these medications.

Research Design Considerations

For several reasons, an RCT is not likely feasible for this research need. Therefore, an alternative approach is to select a sample of adults maintaining the same preventive pharmacologic treatment for over one year and evaluate headache frequency and other outcomes at set intervals throughout their treatment. This design, interrupted time series (without a comparison group) is useful to identify trends in outcomes measures during a long course of treatment. Disadvantages include the limitations in the data available, as much of it will be obtained through the patient record and the potential inconsistencies in data collected over time and between providers.

Chronic Migraine: Third Topical Research Need

- What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)

As with episodic migraine, the optimal duration of preventive pharmacologic treatment is now well understood. Improved understanding should result in improved prescribing behavior. As mentioned previously, scientific evidence does not inform decisions about the optimal treatment duration. This question is relevant for chronic as well as episodic migraine populations.

Research Design Considerations

RCTs are the best option for addressing this research need for reasons previously discussed. Recruiting and retaining sample populations will be especially challenging due to the duration of the intervention. This should be considered when calculating sample size.

Discussion

This FRN project refined and prioritized research needs relevant to the KQs addressed in the CER, “Preventive Pharmacologic Treatments for Migraine.”¹ We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders who represented various perspectives of expertise on the topic. This process identified eight methodological and 22 topical research questions relevant to episodic and chronic migraine. We then asked stakeholders to prioritize research questions according to their potential value. The highly ranked questions were deemed research needs. Stakeholders prioritized three methodological, six episodic migraine topical research questions, and three chronic migraine topical research needs.

Addressing methodological research needs will enhance the utility and comparability of future studies of migraine preventive pharmacologic treatments, specifically for chronic migraine. Identified episodic migraine topical research needs demonstrate the importance of an enhanced understanding the timing of preventive treatments and measuring effectiveness taking the full impact of treatments into account.

Future studies evaluating preventive pharmacologic treatments for episodic and chronic migraine should be designed to pay close attention to reducing bias as much as possible within randomized controlled trials. Double blinding is critical for this topic. Studies should be adequately powered to test hypothesized relationships, including among subgroups. Investigators should consult appropriate guidelines for controlled trials of migraine drugs.^{6,7}

We can make general suggestions for conducting trials to address the efficacy research needs; however, resources in the field offer guidance specific to conducting trials on the pharmacologic prevention of episodic and chronic migraine. The recent update of the “Guidelines for Controlled Trials of Drugs in Migraine” from the IHS Clinical Trials Subcommittee, extensively addresses ideal conduct of trials on preventative pharmacologic interventions specific to episodic migraine.⁷ These guidelines discuss population selection, trial design, results, evaluation, and statistics. The “Guidelines for Controlled Trials of Prophylactic Treatment of Chronic Migraine in Adults” were published in 2008.⁶ A third recently developed resource designed to guide comparative effectiveness research that is helpful to patients making health care decisions is the Preliminary Draft Methodology Report “Our Questions, Our Decisions: Standards for Patient-Centered Outcomes Research” from the Patient-Centered Outcomes Research Institute (PCORI).⁸ Investigators addressing these research needs are urged

to consult the relevant guidelines and reconcile guidelines with PCORI's standards for patient-centered outcomes research when designing studies.

While the variety of perspectives brought by broad stakeholder participation is a strength of this project, we were not able to collect a representative perspective from a larger sample of stakeholders. This is a major limitation. The stakeholders participating in this project were several experts on preventive pharmacologic treatments for episodic and chronic migraine. However, the prioritized research needs reflect the opinions of these stakeholders and may not be applicable to the broader population of stakeholders on this topic.

Conclusions

This FRN project identified several research needs (PICOTS element) thought relevant by a select group of stakeholders to move the field forward:

- How should research of pharmacologic treatment for chronic migraine define treatment success?
- How should chronic migraine populations be defined in trials?
- What biomarkers help predict treatment response?
- What is the optimal duration of preventive pharmacologic treatments for episodic migraine? (T)
- If preventive drug treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels? (I, O)
- What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine? (O)
- What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine? (I)
- Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)
- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)
- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)
- What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)
- What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)

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Background

Context

This Future Research Needs (FRN) project is a followup to the recently completed Comparative Effectiveness Review (CER) “Preventive Pharmacologic Treatments for Migraine.”¹ The review was motivated by uncertainty around the effectiveness, comparative effectiveness, and safety of pharmacologic treatments for the prevention of episodic or chronic migraine in adults. This FRN project identifies and prioritizes specific gaps in the current literature on this topic; additional research would aid decisionmakers.

We used a deliberative process to identify evidence gaps, translate gaps into researchable questions, and solicit stakeholder opinion on the importance of research questions. This report proposes specific research needs along with research design considerations that may help advance research in this field.

Our FRN project identifies research needs within the scope of the CER. CER authors used an analytical framework (Figure 1) to construct the following Key Questions (KQs).

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

Key Question 2

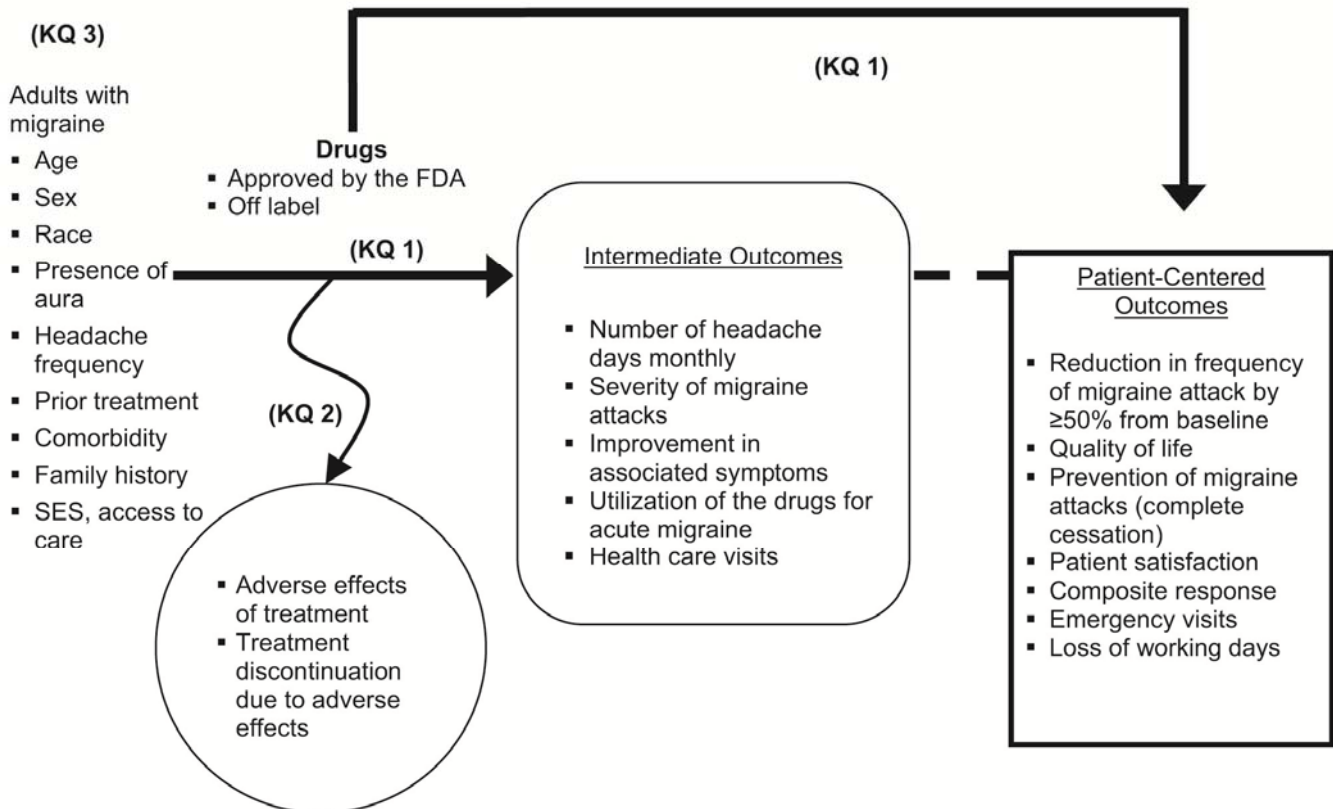
What are the comparative harms from pharmacologic treatments for preventing migraine attacks in adults?

- 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?

Key Question 3

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

Figure 1. Analytic framework



KQ = Key Question; SES = socioeconomic status

Note: 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?

Condition

According to the International Classification of Headache Disorders (ICHD-2), migraine is a common disabling primary headache disorder manifesting in attacks lasting 4 to 72 hours.² Migraine headaches range from moderate to very severe³ and are sometimes debilitating.⁴ Migraine affects 17 percent of women and 6 percent of men.⁵⁻⁸

The ICHD-2 divides migraine into migraine with aura and migraine without aura. The most common type of migraine, migraine without aura, is defined as a headache that occurs at least five times per month with headaches lasting between 4 and 72 hours (untreated or unsuccessfully treated), and having a minimum number of migraine attributes [two of (a) unilateral location, (b) pulsating quality, (c) moderate or severe pain intensity, (d) aggravated by or causing avoidance of physical activity and one of (a) nausea and/or vomiting, (b) phonophobia or photophobia] and cannot be attributed to another condition.

When migraine without aura occurs on 15 or more days per month for at least 3 months and eight of the headaches meet migraine without aura criteria, without medication overuse, the complication of chronic migraine should be diagnosed.⁹ In practice, these definitions have often been simplified as episodic (less than 15 headache days per month) and chronic (15 or more headache days per month). The estimated prevalence of episodic migraine is nearly 12 percent.¹⁰

Chronic migraine affects 1.4 to 2.2 percent of adults.¹¹ All migraine types significantly affect the physical, psychological, and social wellbeing of patients, and can impose serious lifestyle restrictions. Each year lost work time and diminished productivity from migraine costs American employers \$225.8 billion.¹²⁻¹⁴

At a certain level of burden (which can be measured by headache frequency or levels of disability) it may be beneficial to consider preventive pharmacologic treatment. Indications for preventive pharmacologic treatment 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.¹⁵ Some guidelines recommend preventive treatments for patients who have five or more migraine attacks per month,¹⁶ but others suggest it only for those who experience a headache on most days of the month.^{9,17} Forty percent of adults with episodic migraine might benefit from preventive medication;^{6,19,20} yet, only about 12 percent of adults with frequent migraines take preventive medication.^{5,6,19,20}

Preventive medications from several drug classes are thought to affect various aspects of migraine pathophysiology.^{21,22} The U.S. Food and Drug Administration (FDA) has approved four drugs for migraine prevention in adults: the beta blockers propranolol and timolol, and the antiepileptic drugs topiramate and divalproex sodium.²³ For prevention of *chronic* migraine, the FDA has approved only one drug, onabotulinumtoxinA.¹⁸ Providers also commonly prescribe off-label drugs (approved for clinical conditions other than migraine prevention), including off-label antiepileptic drugs, tricyclic antidepressants, and off-label beta blockers.²⁴ However, many other types of drugs have been evaluated for their efficacy in migraine prevention including calcium channel blockers, glutamate blockers, and others.^{23,25}

Preventive pharmacologic treatments aim to eliminate headache pain.²⁶⁻²⁸ Often, however, some degree of pain persists; therefore, treatment success is usually defined by a decrease in migraine frequency of 50 percent or more.³ Preventive treatments are also expected to reduce use of acute drugs and improve quality of life.^{6,29} 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.^{30,31} 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.^{9,26,27,32-36} Often, preventive treatment is recommended for only 6 to 9 months; however, very limited research has examined migraine frequency after discontinuation of preventive treatment.^{3,37}

Findings of the Comparative Effectiveness Review

The CER synthesized data from eligible randomized controlled trials (RCTs) for efficacy and comparative effectiveness. Data from these RCTs and additional eligible nonrandomized studies was synthesized for harms. Key findings are summarized below.¹

Prevention of Chronic Migraine

Efficacy

Only one drug for chronic migraine, onabotulinumtoxinA, was examined in more than one RCT. OnabotulinumtoxinA was better than placebo in reducing monthly migraine attack by 50 percent or more. A single RCT reported that topiramate was better than placebo in achieving a reduction of headache frequency but not better than placebo in reducing monthly migraine attacks by 50 percent or more.

Comparative Effectiveness

Five individual RCTs provided low-strength evidence about the comparative effectiveness of onabotulinumtoxinA versus other drugs for chronic migraine prevention. Individual RCTs examined the comparative effectiveness of onabotulinumtoxinA 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 onabotulinumtoxinA; however, need for acute drugs did not differ between the two. A single RCT examined the comparative effectiveness of onabotulinumtoxinA versus divalproex sodium and found no differences between the two drugs for migraine prevention, migraine-related disability, or quality of life. A single RCT reported that propranolol added to topiramate did not effectively prevent chronic migraine in patients for whom topiramate monotherapy had failed.

Safety

OnabotulinumtoxinA resulted in adverse effects and treatment discontinuation due to adverse effects more often than placebo. Increase in risk of adverse effects was dose responsive. Individual RCTs demonstrated less frequent treatment discontinuation due to adverse effects with onabotulinumtoxinA than topiramate or amitriptyline.

Prevention of Episodic Migraine

All approved drugs were better than placebo in reducing monthly migraine frequency by ≥ 50 percent in individual patients. Rates of clinical response were moderate, 200 to 400 patients per 1,000 treated.

In addition to 50 percent or more 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-blocker metoprolol, and calcium channel blocker nimodipine were better than placebo in reducing monthly migraine attacks by 50 percent or more.

Individual RCTs demonstrated that the off-label anti-epileptics carbamazepin and valproate (but not acetazolamide, lamotrigine, or oxcarbazepine) were better than placebo in reducing monthly migraine attacks by 50 percent or more. Individual RCTs demonstrated that off-label beta blockers acebutolol atenolol and nadolol (but not pindolol or alprenolol) were better than placebo in reducing monthly migraine attacks by 50 percent or more.

Individual RCTs of off-label angiotensin converting enzyme (ACE) inhibiting drugs demonstrated promising results. The ACE 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, improvement in Headache Index by ≥ 50 percent, and 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 off-label angiotensin II antagonist (ARB) candesartan was better than placebo in achieving a clinical response defined as 50 percent or more reduction in migraine days. Candesartan also decreased migraine-related disability but had no effect on use of drugs for acute migraine attacks. In contrast, ARB telmisartan was not better than placebo in reducing monthly migraine attacks by 50 percent or more.

Pooled analysis was possible for only four paired drug comparisons for the prevention of episodic migraine. The analyses demonstrated few significant differences between individual drugs.

Safety

Bothersome adverse effects leading to treatment discontinuation were greater than placebo for topiramate in doses of 100 and 200 mg/day (but not 50 mg/day) and propranolol.

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.

In direct comparisons of divalproex or valproate versus placebo, treatment discontinuation due to adverse effects did not differ. Pooled analysis showed no differences in treatment discontinuation with topiramate versus amitriptyline.

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. A network meta-analysis indicated that off-label ACE inhibitors and beta-blockers were the safest treatment option for adults with episodic migraine.

Patient Characteristics

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

- OnabotulinumtoxinA 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 depression or with baseline frequent and severe migraine.
- Topiramate was more likely to reduce migraine attacks in women but not in men according to one low-risk-of-bias RCT.
- Several post hoc subgroup analyses of topiramate versus placebo provided inconsistent evidence of the drug efficacy in respect to aura.

Objective

Our FRN project identifies and prioritizes research needs arising from the status of current literature on efficacy, comparative effectiveness, and safety of preventative pharmacologic treatments in adults for the prevention of episodic or chronic migraine. These research needs are presented along with research design considerations and represent the opinion of a select group of stakeholders on issues on which future research has potential value to the current body of evidence.

Evidence Gaps and Research Question Development

The CER identified gaps and biases in available evidence and made future research recommendations. Findings from the CER drew conclusions about the efficacy and comparative effectiveness of the off-label use of ACE inhibitors and angiotensin II blockers for migraine prevention that were stronger than current guidelines suggest. Because these conclusions were drawn from a small number of RCTs, future research could refute or validate the results of these early studies, assisting decisionmakers.

Additionally, well-designed randomized head-to-head clinical trials should examine the comparative effectiveness of approved drugs and the most effective off-label ACE inhibitors, angiotensin II blockers, antidepressants, and 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. The long-term efficacy of most preventive pharmacologic treatments is unknown. Evidence on improving quality of life was inconsistent across individual drugs. While common in practice, evidence for tailoring treatment to the individual patient is very limited. Future studies should strive to better capture adverse effects associated with migraine preventive drugs. Additionally, future research synthesis would benefit from trial registration and posting of results in [Clinicaltrials.gov](https://clinicaltrials.gov). We translated the list of Future Research Needs from the CER into researchable questions (Table 1).

Table 1. Evidence gap research questions

Methodological Research Questions	
	<ul style="list-style-type: none"> • How should treatment success be defined in research on pharmacologic treatment of episodic migraine? • How should treatment success be defined in research on pharmacologic treatment of chronic migraine? • What is the minimal clinically important difference for the Migraine Disability Assessment questionnaire scores? • How should drug adverse effects be addressed in research?
Topical Research Questions (PICOTS Element)	
Benefits of Treatment	<p><u>Episodic Migraine</u></p> <ul style="list-style-type: none"> • What is the efficacy of angiotensin acting drugs in the prevention of episodic_migraine? • What is the comparative effectiveness (head to head trials) between angiotensin acting drugs, beta blockers, and antiepileptics for prevention of episodic migraine? (I, C) • What is the comparative effectiveness (head to head trials) of pharmacologic treatments in terms of validated measures of quality of life and migraine related disability for prevention of episodic migraine? (O) • What is the comparative effectiveness (head to head trials) of pharmacologic treatments on health care utilization (emergency department visits, hospitalizations, abortive drug utilization and overuse) for episodic migraine? (O) • What is the dose response relationship in reducing occurrence and severity of episodic migraine? (I, O) • What is the long-term (>1 year) effectiveness of pharmacologic treatments for prevention of episodic migraine? (O) • Are combinations of pharmacologic treatments effective in patients for whom pharmacologic treatments with a single preventative drug are not effective or tolerable in the prevention of episodic migraine? (I) • If drug treatment for prevention of episodic migraine is effective then discontinued, what is the likelihood of the return to previous levels of episodic migraine? <p><u>Chronic Migraine</u></p> <ul style="list-style-type: none"> • What is the efficacy of angiotensin acting drugs in the prevention of chronic_migraine? • What is the comparative effectiveness (head to head trials) between angiotensin acting drugs, beta blockers, and antiepileptics in the prevention of chronic migraine? (I, C) • What is the comparative effectiveness (head to head trials) of pharmacologic treatments in terms of validated measures of quality of life and migraine related disability for prevention of chronic migraine? (O) • What is the comparative effectiveness (head to head trials) of pharmacologic treatments on health care utilization (emergency visits, hospitalizations, abortive drug utilization and overuse) for chronic migraine? (O) • What is the dose response relationship in reducing occurrence and severity for prevention of chronic migraine? (I, O) • What is the long-term (>1 year) effectiveness of pharmacologic treatments for prevention of chronic migraine? (O) • Are combinations of pharmacologic treatments effective for prevention of chronic migraine in patients for whom pharmacologic treatments with a single preventative drug are not effective or tolerable? (I) • If drug treatment is effective in the prevention of chronic migraine but discontinued, what is the likelihood of the return to previous levels of chronic migraine?

Table 1. Evidence gap research questions (continued)

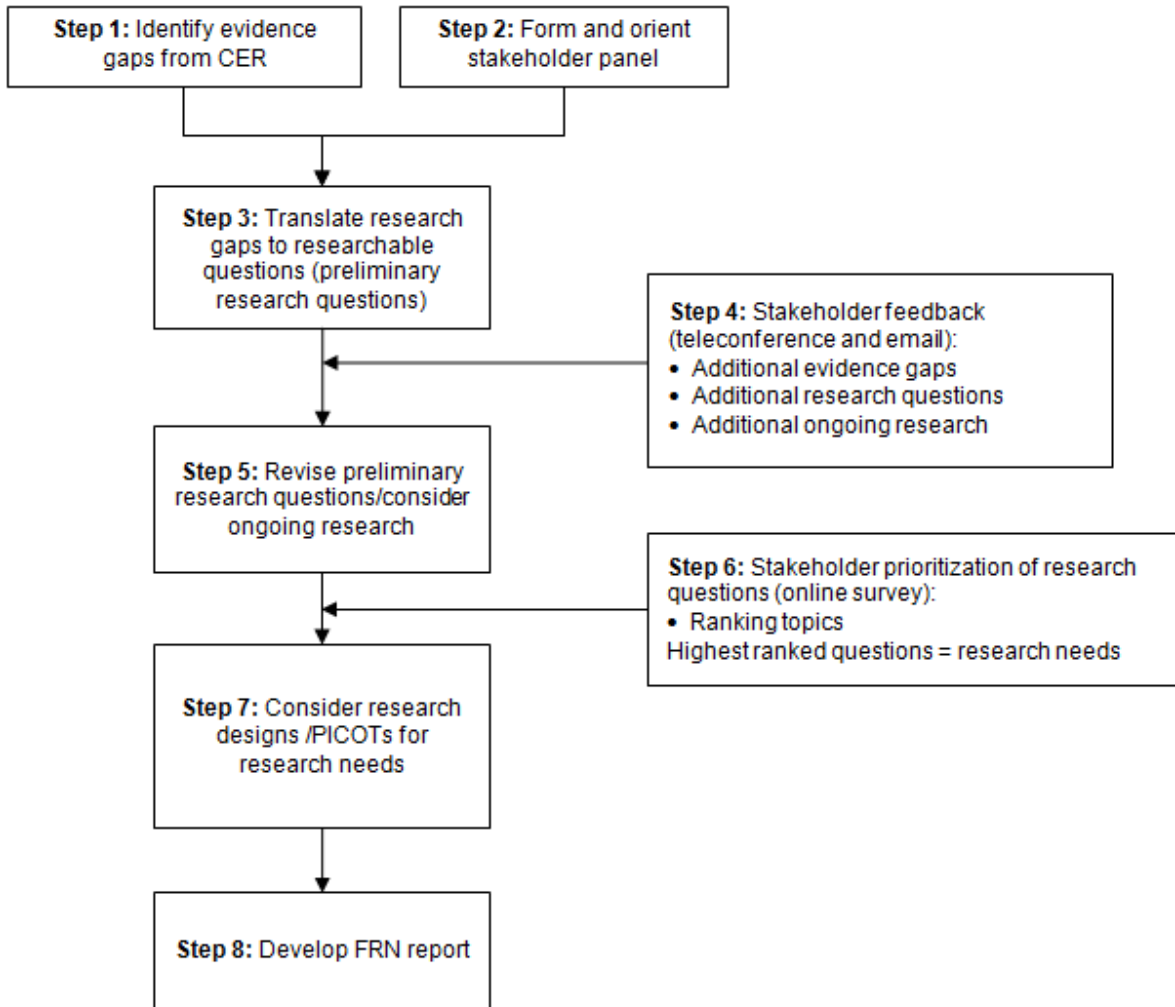
<i>Topical Research Questions (PICOTS Element) (continued)</i>	
Harms of Treatment	<p><u>Episodic Migraine</u></p> <ul style="list-style-type: none"> • What are the comparative harms (head-to-head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for prevention of episodic migraine? (I, C) • What is the dose response relationship on harms for prevention of episodic migraine? (I, O) • What is the long-term (> 1 year) safety of pharmacologic treatments for prevention of episodic migraine? (O) <p><u>Chronic Migraine</u></p> <ul style="list-style-type: none"> • What are the comparative harms (head-to-head trials) between angiotensin acting drugs and beta blockers and approved antiepileptics for prevention of chronic migraine? (I, C) • What is the dose response relationship for effective drugs on harms for prevention of chronic migraine? (I, O) • What is the long-term (>1 year) safety of pharmacologic treatments for prevention of chronic migraine? (O)
Benefits/ Harms Patient Subgroups	<p><u>Episodic Migraine</u></p> <ul style="list-style-type: none"> • What is the comparative effectiveness (head to head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for prevention of episodic migraine in different patient subpopulations? (P) • What are the comparative harms (head to head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for prevention of episodic migraine in different patient subpopulations? (P) <p><u>Chronic Migraine</u></p> <ul style="list-style-type: none"> • What is the comparative effectiveness (head-to-head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for prevention of chronic migraine in different patient subpopulations? (P) • What are the comparative harms (head-to-head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for prevention of chronic migraine in different patient subpopulations? (P)

PICOTS = population, intervention, comparison, outcome, timing, and setting.

Methods

We used a deliberative process to refine, add, and prioritize research questions to arrive at research needs relevant to the evidence gaps identified in the recently completed CER, “Preventive Pharmacologic Treatments for Migraine.”¹ Figure 2 illustrates the eight steps used to accomplish these objectives.

Figure 2. Project flow



CER = Comparative Effectiveness Review; FRN = Future Research Needs; PICOTS = Population, intervention, comparison, outcome, timing, and setting

Engagement of Stakeholders

We recruited a diverse stakeholder panel whose members represented various perspectives relevant to the topic. We followed guidance on stakeholder engagement for recruitment and communication.³⁸ We sought to recruit stakeholders who were actively interested in preventive pharmacologic treatments for migraine and who wished to help shape future research priorities. We identified potential stakeholders via several means. We sought recommendations from the

CER project team; we invited select Key Informants and Technical Expert Panel members and reviewed recent literature to identify additional experts on the topic.

Research representatives were national experts who were familiar with: (1) evidence-based medicine; (2) the obstacles often associated with conducting well-designed research; and (3) preventive pharmacologic treatments for migraine from the fields of neurology and pharmacy. We invited participation from the National Institute of Neurological Disorders and Stroke (NINDS), which supports and conducts relevant research. We engaged providers and consumers because the decisional dilemmas faced by these groups are critical to identifying and prioritizing research questions. Many stakeholders were also involved in the CER process as Key Informants, Technical Expert Panel members, or peer reviewers. This made engaging them as stakeholders challenging, because the timing of the FRN project overlapped with finalization of the CER. However, these stakeholders had the advantage of familiarity with the CER.

Handling Conflicts of Interest

We collected disclosures of conflicts of interests from all stakeholders. Disclosed interests did not bar any stakeholders from participation but allowed the Evidence-based Practice Center (EPC) to evaluate contributions based upon possible conflicts. Stakeholders used a web-based survey to rank research questions during the prioritization exercise, thus researchers and funders were blind to the others' stated opinions.

Refinement of Research Questions

We provided stakeholder panel members with a preliminary set of research questions prior to conference calls. During conference calls, we sought stakeholder input to further refine the research questions (i.e., organization and wording of the questions, identification of additional research questions, and elimination of research questions with limited clinical value). To facilitate this input, we provided stakeholders in advance with the draft CER Executive Summary to provide relevant background to the project. We conducted three conference calls with available stakeholders during June 2012. A total of 12 stakeholders participated in the calls. All participants provided input on the calls. We revised the preliminary questions based on these discussions.

We also revised the preliminary questions in light of recent and ongoing work. For instance, the NINDS Common Data Elements project for headache has addressed several of the limitations CER authors found in the current literature concerning poor reporting of patient and disease characteristics.³⁹ We therefore excluded those questions from the ranking process. The revised set of research questions for prioritization appears in Appendix A.

Prioritization

Our stakeholders were asked to prioritize these research questions according to specified criteria based on the potential impact of future research addressing each question. These criteria have been operationalized into seven components specific to EPC FRN projects. These components, called "Potential Value Criteria," are as follows:⁴⁰

- Potential for significant health impact on the current and future health status of people with respect to burden of the disease and health outcomes: mortality, morbidity, and quality of life.

- Potential to reduce important inappropriate (or unexplained) variation in clinical practices known to relate to quality of care. Potential to resolve controversy or dilemmas in what constitutes appropriate health care. Potential to improve decisionmaking for patient or provider, by decreasing uncertainty.
- Potential for significant (nontrivial) economic impact related to the costs of health service: to reduce unnecessary or excessive costs; to reduce high costs due to high volume use; to reduce high costs due to high unit cost or aggregate cost. Costs may impact consumers, patients, health care systems, or payers.
- Potential risk from inaction: Unintended harms from lack of prioritization of proposed research; opportunity cost of inaction.
- Addresses inequities, vulnerable, diverse populations (including issues for patient subgroups); potential to reduce health inequities.
- Potential to allow assessment of ethical, legal, social issues pertaining to the condition.
- Potential for new knowledge (research would not be redundant; question not sufficiently researched, including completed and in-process research; utility of available evidence limited by changes in practice, e.g., disease detection or evolution in technology).

To collect these prioritizations, we developed a web-based survey using prioritization software developed by the Research Triangle Institute-University of North Carolina Evidence-based Practice Center to collect stakeholder prioritization of the research gap questions.⁴¹ Ten stakeholders who completed disclosure statements (less than 10 were non-Federal employees) were invited to rank research questions identified via the stakeholder conference calls. These stakeholders were instructed to assign stars to research questions in three groups (methodological research questions, topical research questions addressing episodic migraine, topical research questions addressing chronic migraine).

Stakeholders' cumulative star count was used to rank the research questions in each group. We identified natural breakpoints in the prioritizations that separated high, moderate, and low-priority research questions. Highly prioritized research questions were considered research needs.

We then evaluated the feasibility criteria for research needs. We framed feasibility in terms of anticipated research designs. For example, factors that affect the feasibility of conducting randomized controlled trials include the sample size needed for the outcome, the size of the available pool of potential subjects, followup duration, willingness to randomize, and applicability issues. In contrast to randomization and applicability, observational studies face feasibility issues related to measuring study variables with different data sources and unobserved variables that create risk of bias.

Research Design Considerations

We generated research design considerations for identified research needs. For methodological research needs, we provided context and described resources and research design considerations potentially useful to researchers, facilitators, and funders of this type of research. For topical research needs, we highlighted the relevant element(s) of the PICOTS (population, intervention, comparison, outcome, timing, and setting), provided context, described related ongoing research, and discussed potential research designs. Research design considerations were guided by a recent Agency for Healthcare Research and Quality (AHRQ) report describing frameworks for research design considerations for Future Research Needs.⁴² We did not consult with stakeholders for input on research design considerations.

Results

Research Needs

Prioritization Results

Stakeholders separately prioritized three groups of questions (methodological, episodic migraine, and chronic migraine). Of the 10 stakeholders invited to participate in the prioritization process, six prioritized methodological research questions, seven prioritized episodic migraine topical research questions, and six prioritized chronic migraine topical research questions. We analyzed cumulative prioritizations (total number of stars assigned to each question) for each group of research questions to identify natural breakpoints (Tables 2–4). High-priority research questions were deemed research needs.

Ongoing Studies

We conducted a search for ongoing studies in ClinicalTrials.gov (search strategy appears in Appendix B). Our search identified 163 studies. Thirty-two of these studies (Appendix C) were either completed but not yet published or ongoing and relevant to the scope of the CER. These studies will provide valuable information; however, it is unclear whether the recently completed or currently ongoing studies will sufficiently address identified future research questions. Therefore, our research questions were not revised based upon these ongoing studies. We discuss those relevant to identified research needs.

Table 2. Stakeholder prioritization of methodological research questions

Tier	Research Question Cumulative Ranking (n=6)	Total Stars	Number Stakeholders Prioritizing
Tier 1: High Priority	How should research of pharmacologic treatment for chronic migraine define treatment success?	4	3
	How should chronic migraine populations be defined in trials?	4	2
	What biomarkers help predict treatment response?	4	2
Tier 2: Moderate Priority	How should research of pharmacologic treatments for episodic migraine define treatment success?	3	3
	How should adverse effects be measured and reported in pharmacologic studies for the prevention of chronic and/or episodic migraine?	3	2
	Should episodic and chronic migraine be treated as one progressive disease or as conditions arising from separate physiological mechanisms?	3	2
Tier 2: Low Priority	What is the appropriate timing to evaluate treatment success or failure for each drug/class of drug for preventing chronic and/or episodic migraine?	2	2
Tier 4: Not Prioritized by Stakeholders	What is the minimal clinically important difference for the Migraine Disability Assessment questionnaire scores?	0	0

Table 3. Stakeholder prioritization of episodic migraine research questions

Tier	Research Question (PICOTS element) Cumulative Ranking (n=7)	Total Stars	Number Prioritizing
Tier 1: High Priority	What is the optimal duration of preventive pharmacologic treatments for episodic migraine? (T)	5	4
	If preventive drug treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels? (I, O)	5	4
	What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine? (O)	4	3
	What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine? (I)	4	4
	Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)	4	3
	Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)	4	4
Tier 2: Moderate Priority	What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for episodic migraine? (O)	3	2
	What is the efficacy of angiotensin acting drugs (ACE inhibitors, angiotensin receptor blockers) in preventing episodic migraine?	2	1
	What is the efficacy of preventive pharmacologic treatments for episodic migraine combined with treatment of existing comorbidities? (P, I)	2	2
	What is the comparative effectiveness (head-to-head trials) of angiotensin acting drugs, beta blockers, [antidepressants], and antiepileptics in preventing episodic migraine? (I, C)	2	2
	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for episodic migraine in terms of validated measures of quality of life and migraine-related disability? (O)	2	1
	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for episodic migraine with regard to health care utilization (emergency department visits, hospitalizations, acute drug utilization, mental health visits, and medication overuse)? (O)	2	2
	What is the mechanism of action for drugs from each pharmacologic class used for episodic migraine prevention? (I)	2	1
What is the long-term (>1 year) safety of preventive pharmacologic treatments for episodic migraine? (O)	2	1	
Tier 3: Low Priority	What is the dose-response relationship with regard to migraine occurrence and severity from preventive pharmacologic treatments for episodic migraine? (I, O)	1	1
	What are the comparative harms (head-to-head trials) of angiotensin acting drugs, beta blockers, [antidepressants], and antiepileptics for preventing episodic migraine? (I, C)	1	1
	What is the dose response relationship with regard to harms from preventive pharmacologic treatments for episodic migraine? (I, O)	1	1
	What is the efficacy of preventive pharmacologic treatments in preventing episodic migraine in patient subgroups? (P)	1	1
	What is the comparative effectiveness (head-to-head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for preventing episodic migraine in patient subgroups? (P)	1	1
	What are the comparative harms (head-to-head trials) of angiotensin acting drugs, beta blockers, antidepressants, and approved antiepileptics for preventing episodic migraine in patient subgroups? (P)	1	1
Tier 4: Not Prioritized by Stakeholders	How does patient compliance with pharmacologic treatment for episodic migraine affect efficacy? (P)	0	0

PICOTS = Population, intervention, comparison, outcome, timing, and setting

Table 4. Stakeholder prioritization of chronic migraine research questions

Tier	Research Question Cumulative Ranking (n=7)	Total Stars	Number Prioritizing
Tier 1: High Priority	Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)	7	4
	What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)	6	5
	What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)	5	4
Tier 2: Moderate Priority	Are combinations of pharmacologic treatments effective in preventing chronic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable?(I)	4	4
	If preventive drug treatment for chronic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels? (I, O)	4	4
	What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing chronic migraine? (O)	3	3
	What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing chronic migraine? (I)	3	3
Tier 3: Low Priority	What is the comparative effectiveness (head-to-head trials) of antihypertensives acting drugs, beta blockers, [antidepressants], and antiepileptics in preventing chronic migraine? (I, C)	2	2
	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for chronic migraine with regard to health care utilization (emergency department visits, hospitalizations, acute drug utilization, mental health visits, and medication overuse)?(O)	2	2
	What are the comparative harms (head-to-head trials) of antihypertensives acting drugs, beta blockers, antidepressants, and approved antiepileptics for preventing chronic migraine in patient subgroups? (P)	2	2
	What is the efficacy of preventive pharmacologic treatments in preventing chronic migraine in patient subgroups? (P)	2	2
	What is the efficacy of preventive pharmacologic treatments for chronic migraine combined with treatment of existing comorbidities? (P, I)	1	1
	What is the dose-response relationship with regard to migraine occurrence and severity from preventive pharmacologic treatments for chronic migraine? (I, O)	1	1
Tier 4: Not Prioritized by Stakeholders	What is the efficacy of antihypertensives acting drugs (ACE inhibitors, antihypertensives receptor blockers) in preventing chronic migraine?	0	0
	How does patient compliance with pharmacologic treatment for chronic migraine affect efficacy? (P)	0	0
	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for chronic migraine in terms of validated measures of quality of life and migraine-related disability? (O)	0	0
	What is the mechanism of action for drugs from each pharmacologic class used for chronic migraine prevention? (I)		
	What is the dose-response relationship with regard to harms from preventive pharmacologic treatments for chronic migraine? (I, O)		
	What is the long-term (>1 year) safety of preventive pharmacologic treatments for chronic migraine? (O)	0	0
	What is the comparative effectiveness (head-to-head trials) of antihypertensives acting drugs, beta blockers, and approved antiepileptics for preventing chronic migraine in patient subgroups? (P)	0	0
	What are the comparative harms (head-to-head trials) of antihypertensives acting drugs, beta blockers, and approved antiepileptics for preventing chronic migraine in patient subgroups? (P)	0	0

PICOTS=Population, intervention, comparison, outcome, timing, and setting

Methodological Research Needs

Three of the eight methodological research questions received five or more stars and were thus the top three research questions according to our stakeholders. We designated these as our methodological research needs:

- How should research of pharmacologic treatment for chronic migraine define treatment success?
- How should chronic migraine populations be defined in trials?
- What biomarkers help predict treatment response?

Addressing these methodological research needs will enhance the utility and translation of current and future research on pharmacologic treatments for the prevention of episodic or chronic migraine in adults. Methodological issues surrounding the study of chronic migraine were of utmost importance to stakeholders. This is likely due to the fact that the classification of chronic migraine by the International Headache Society (IHS) is relatively recent⁴³ (although recognition and definition of the condition, then termed “transformed migraine,” began in the 1980s).

Additionally, classifications thus far have proved controversial. Chronic migraine was first classified by the IHS in ICHD-2 in 2004. This definition (1) was much stricter than had been described in previous literature; (2) did not correlate well with populations fitting the transformed migraine definition; and (3) was complicated in practice. Thus, it was revised in 2006.²⁶ The 2006 revision was considerably broader, but nonetheless proved problematic in terms of defining chronic migraine populations in trials, clinical practice, and epidemiological studies. Lack of a consistent definition remains an obstacle to interpretation and synthesis of chronic migraine research.⁴³ This in part explains our stakeholders’ major concern about reaching a consensus definition for chronic migraine populations. Whether consensus can be achieved prior to publication of the upcoming ICHD-3, expected in 2013,⁴⁴ remains to be seen.

Operationalizing treatment success of preventive pharmacologic treatments for chronic migraine was identified as a research need despite current related consensus work. The NINDS Headache Common Data Element (CDE) Project recently released recommendations from the Headache Preventive Therapies Subgroup for measuring outcomes in headache trials.³⁹ These recommendations were not specific to chronic migraine, and the population of chronic migraine patients is a small proportion of those with headache. Therefore stakeholders may have believed that specific discussion should address outcomes for chronic migraine patients.

The third methodological research need addresses particular biomarkers that may be associated with treatment response. Identifying biomarkers in migraine received important recognition in a special issue of “Headache” in 2006.⁴⁵ Our stakeholders provided an indication that despite research on biomarkers since that special issue, important questions remain, especially with regard to how biomarkers could potentially help patients and clinicians make informed choices about preventive treatments.

Considerations for Potential Research

These methodological research needs could be addressed through consensus development, additional systematic reviews, post hoc analyses of previous trial data, and/or qualitative research. One way to identify outcomes specifically valued by chronic migraine patients may involve beginning where the CDE Headache Preventive Therapies group left off.³⁹ The

knowledge of this workgroup gained while selecting measures for headache in general likely offers direction to identifying potential measures specific to migraine.

Reviewing the literature for reports of patient opinions or preferences may also provide background. Qualitative research might also contribute. For example, by using focus groups with patients with chronic migraine and their families, employers would help to identify patient-centered outcomes. Preferred outcomes are likely associated with current condition severity and treatment burden.

Arriving at a consensus definition of chronic migraine that is easily implemented in trials and translates well to clinical practice has been shown to be a challenging task. However, continued consultations among researchers and providers along with continued field testing of various definitions⁴⁶ should ultimately produce a definition that is meaningful, feasible, and useful for research and practice.

Identifying biomarkers that can be reliably used to assist in predictions of preventive pharmacologic treatment response would greatly assist decision makers. While research continues to identify these markers, synthesizing the current state of knowledge on this topic could help to identify specific directions to next approach. Knowledge could also be gained through post hoc analysis of previous trial data to explore potential relationships.

Topical Research Needs

Natural breakpoints in weighted rankings revealed six prominent topical research needs relevant to episodic migraine and three relevant to chronic migraine. Topical research needs addressed a range of PICOTS elements including the population, intervention, outcome, and timing. Stakeholders did not prioritize basic efficacy questions that have been studied in numerous trials. Nor did they prioritize questions about the comparative effectiveness of different treatments. They were most interested in identifying specific details about these efficacious treatments that can better inform practice decisions and communication with patients. Although most of these research needs were directly addressed by the CER, two research needs were tangential to the CER KQs. Those addressed by the CER remain research needs because the evidence on these specific questions was insufficient or lacked strength.

Episodic Migraine: First Topical Research Need

- What is the optimal duration of preventive pharmacologic treatments for episodic migraine?

The CER addressed this research need with a question examining the influence of dose and duration of treatment on patient-centered outcomes (KQ 1e). The studies identified for this KQ examined different doses of the drugs and measured outcomes at 2 to 3 months of followup. The short timeframes analyzed in trials along with some guidance suggesting that successful preventive drugs be taken for “3 to 6 months” or for “several months”⁴⁷ seem to contradict the nature of the condition and the length of treatment that occurs in practice. Limited research exists regarding migraine frequency after discontinuation of preventive treatment.³ The CER did not find good evidence for long-term effectiveness and safety with preventive drugs.

The recent guideline report from the Canadian Headache Society addressed the question of how long to continue preventive treatment, concluding that little evidence is available to inform these decisions. They recommended that tapering and discontinuing preventive medications be considered after 6 to 12 months of successful treatment.⁴⁷ Stakeholders agreed that the ideal time to treat patients with preventive pharmacologic treatments it is not well understood. Future

studies testing these longer timeframes for discontinuing preventive pharmacologic treatment would inform clinical practice.

Research Design Considerations

Studies of the efficacy or comparative effectiveness of preventive pharmacologic treatments for migraine need to use experimental designs to achieve valid results. These studies will likely test a hypothesis that longer durations of preventive treatment are more effective than shorter durations. Therefore, studies should include groups of patients with variation in treatment duration in order to test the hypothesis by identifying differences in outcomes between groups. These treatment-related research questions are most appropriately studied with adequately powered double-blind randomized controlled trials. Double blinding is critical for several reasons. First, the nature of the condition relies on patient report and provider judgment for diagnosis and therefore inclusion in intervention studies, as opposed to conditions that use definitive lab values for diagnosis. Second, outcomes used to measure effectiveness are also subjective and self-reported. The large placebo response observed in studies on this topic creates another strong indication that blinding is essential to the validity of studies on this topic.

In addition to blinding, an RCT designed to identify the optimal duration of preventive pharmacologic treatment should pay particular attention to subgroups. Optimal duration of treatment likely varies according to certain patient and migraine characteristics. Therefore, these subgroups need to be identified when the RCT is planned and power calculations should be conducted to insure adequate subgroup sample sizes. Detailed study design considerations regarding the conduct of RCTs to address this research need are described in Table 5.

Table 5. Episodic migraine: design considerations for first topical research need

Research Question: What is the optimal duration of preventive pharmacologic treatments for episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to preventive pharmacologic treatments of varying duration.
Population	Adults with episodic migraine.
Intervention	Active preventive pharmacologic treatment (i.e. tricyclic antidepressant) for 6, 9, or 12 months followed by placebo.
Comparator	Preventive pharmacologic treatment (i.e. tricyclic antidepressant) for 3 months followed by placebo.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days
Timing	Outcomes measurement should extend through at least one-year from cessation of pharmacologic treatment; longer follow-up would be clinically valuable.
Setting	Headache clinic
Advantages for Producing a Valid Result	This design is likely to produce the most valid results. Blinding is necessary to insure validity. Analysis of specific subgroups identified a priori would enhance the clinical usefulness and generalizability.
Resource use, size and duration	Necessary to recruit large samples and follow for significant length of time; power calculation with planned subgroup analysis should be conducted to determine appropriate sample size.
Ethical, legal, and social issues	Ethical challenges are expected to be minimal. Harms related to longterm use of preventive pharmacologic treatments for migraine unclear; however most drugs used long term for other conditions.
Availability of data/ability to recruit	Fair. Condition is fairly prevalent and preventive pharmacologic treatments are standard care with harms that are not typically life-threatening. Intervention requires significant time commitment from patients, but no other significant recruitment problems are expected.

Episodic Migraine: Second Topical Research Need

- If preventive pharmacologic treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels?

This research need was not specifically addressed within the KQs of the CER, but relates to treatment duration addressed in KQ 1e and the previous research need (Episodic Migraine: First Topical Research Need). A recent review discusses the few studies that have evaluated discontinuation after successful short courses of preventive drugs (topiramate, valproate, and flunarizine) and reports that relapse does occur in most patients.⁴⁷ Stakeholders agreed that an improved understanding of the consequences of discontinuing treatment was needed.

Research Design Considerations

This question could be considered a subquestion in an RCT addressing the first research need regarding optimal duration of treatment. However, a more clinically meaningful population in which to analyze outcomes after discontinuing treatment would be those treated successfully with a preventive pharmacologic treatment for which treatment was discontinued treatment based on some objective clinical measure, as opposed to time frame alone.

An observational study design could be used to evaluate the effects of discontinuing preventive pharmacologic treatment in this population. Patients achieving success with treatment and ready to discontinue treatment could be recruited and followed over time, and their headache frequency could be assessed at multiple intervals. Table 6 describes research design considerations relevant to this research need. As with the previous research need, subgroups based upon patient or disease characteristics (i.e., length of time with episodic migraine, comorbidities) are likely important correlates of post treatment headache treatment and studies designed to test specific subgroups of patients will be most valuable.

Table 6. Episodic migraine: design considerations for second topical research need

Research Question: If preventive drug treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels?	
Considerations	Interrupted Time Series (Without a Comparison Group)
Design Description	A cohort of individuals successfully completing a course of preventive pharmacologic treatment selected and followed over time to determine if episodic migraine returns to previous levels.
Population	Individuals successfully treated for episodic migraine and discontinuing preventive pharmacologic treatment.
Intervention	Migraine frequency at specified intervals after discontinuing treatment
Comparator	Migraine frequency during active treatment
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days
Timing	Individuals followed for several months to years.
Setting	Headache clinic
Advantages for Producing a Valid Result	Because there is no intervention and therefore no concerns about selection bias, results should be valid. However, results are likely related to specific patient and disease characteristics so a large sample capable of testing subgroup differences is necessary to provide the most clinically valuable information. It will be necessary to perform power calculations to determine sufficient sample size within each a priori identified subgroup. Important to have baseline data on headache frequency prior to pharmacologic treatment for comparison purposes. Implications about whether and how the large placebo effect observed in efficacy trials for preventive pharmacologic treatments might influence results should be considered. Results may only be generalizable only to population that discontinues treatment as defined in study.
Resource use, size and duration	Resource requirements are high because a large sample size and long-term followup are necessary to provide clinically useful information.
Ethical, legal, and social issues	Minimal.
Availability of data/ability to recruit	Recruitment/data should be fairly easy to obtain. Efforts to maintain the sample over course of study will be necessary.

Episodic Migraine: Third Topical Research Need

- What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine?

CER investigators identified several RCTs that examined quality of life, however judged that the evidence lacked the strength necessary for robust conclusions and merited future research. Specifically, few studies assessed the clinical importance of the changes in quality of life or disability scales. The CER does discuss results from several trials that analyzed quality of life types of outcomes (as measured with a variety of scales) and suggests that preventive treatment typically improved quality of life (topiramate, divalproex). While use of acute medications is a commonly used outcome in episodic migraine trials, other health care use outcomes such as emergency department visits were not often included.

Our stakeholders agreed that the currently available evidence does not adequately measure the true burden of preventative pharmacologic treatments for episodic migraine. For instance, a treatment that decreases headache frequency by 50 percent may not be perceived as an improvement if patients become so fatigued or nauseous that they are still unable participate in social roles and activities. Therefore, additional efficacy trials with outcomes measured using validated quality of life measures would provide a clearer indication of the true benefit of preventive medications. Future research is needed to address efficacy, comparative effectiveness, and safety in terms of the net impact on patients' lives.

Research Design Considerations

As we previously mentioned, migraine prevention efficacy is best studied with appropriately powered double-blind randomized controlled trials. Trials to address this research need will be similar to trials that have been previously conducted, but using additional patient-centered outcomes. Table 7 describes specific considerations for designing trials to assess these outcomes.

Table 7. Episodic migraine: design considerations for third topical research need

Research Question: What is the efficacy of preventive pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to preventive pharmacologic treatments and follow over time.
Population	Adults with episodic migraine.
Intervention	Preventive pharmacologic treatments.
Comparator	Placebo.
Outcomes	Quality of life, migraine-related disability, health care utilization.
Timing	Followup should extend through duration of treatment.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is necessary to produce valid results. However, measurement of subjective outcomes and interpretation of changes in scale scores presents limitations. Blinding is necessary to insure validity.
Resource use, size and duration	High; large sample sizes to test differences among subgroups would provide most clinically meaningful information.
Ethical, legal, and social issues	Ethical challenges exist. Randomization to placebo may be considered inadequate care. Harms related to intervention not typically life threatening.
Availability of data/ability to recruit	Moderate. Intervention requires time commitment from participants; participants may be unwilling to be randomized to placebo.

Episodic Migraine: Fourth Topical Research Need

- What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine?

Current clinical practice for migraine prevention often involves multimodal treatments (a combination of pharmacologic, psychological, lifestyle, cognitive, and other interventions). How well these combined treatments work, the marginal benefits above pharmacologic treatments alone, and in which patients they offer a greater benefit over pharmacologic treatments alone needs improved understanding. The four studies evaluating multimodal treatments analyzed in the CER suggested that these programs may offer benefits beyond preventive pharmacologic treatments alone. Stakeholders suggested the need for additional research to address these programs be conducted with precise intervention definitions or protocols, and assessments of how they work and with which patients.

Research Design Considerations

RCTs that assess the efficacy of these combined interventions would add value to the current body of evidence. Studies addressing this research need will test the hypothesis that multimodal treatments are superior to preventive pharmacologic treatments. The most important multimodal treatments to test are those commonly used in practice and are likely to include a preventive medication along with some type of behavioral therapy as compared with medication as the only preventive treatment. Therefore, the most important trials to address this research need are large comparative effectiveness trials with a diverse set of participants and sample sizes of subgroups of patients sufficient to test subgroup effects. Specific research design considerations for these trials are described in Table 8.

Table 8. Episodic migraine: design considerations for fourth topical research need

Research Question: What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to either multimodal treatments (combination of pharmacologic, behavioral, etc. treatments) or a single mode of treatment (e.g., pharmacologic only) and follow them over time to measure efficacy in preventing episodic migraine.
Population	Adults with episodic migraine.
Intervention	Multimodal treatments typically used in practice (combination of pharmacologic, behavioral, etc. treatments).
Comparator	Single mode of preventive treatment (pharmacologic only).
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Studies of treatment duration of at least 6 months will provide the most clinically useful information.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is necessary to produce the valid results. Blinding is necessary to insure validity. Generalizability may be low.
Resource use, size and duration	High; large sample sizes to test differences among subgroups would provide most clinically meaningful information; likely necessary to recruit large samples and follow for significant length of time.
Ethical, legal, and social issues	Ethical challenges exist. However, both arms involve standard treatment that is not invasive and harms are not typically life threatening.
Availability of data/ability to recruit	Fair, condition has fairly high prevalence.

Episodic Migraine: Fifth Topical Research Need

- Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)

This research need addresses combinations of preventive medications, while the previous question addressed combinations of different types of treatments. Combinations of preventive pharmacologic treatments are used for episodic migraine in some circumstances. The CER does not draw conclusions about the efficacy or comparative effectiveness of drug combinations across classes for prevention of episodic migraine. However, combinations are often used in practice especially in patients with refractory migraine (failed treatment with one drug alone).⁴⁷ Patients that cannot tolerate certain drugs at necessary dosage might better tolerate combination of drugs at lower doses. While evidence about combination preventive medication treatment is not available from blinded RCTs, several open label trials suggest that preventive drug combinations may be effective when treatment with a single drug has failed.⁴⁷ Stakeholders are interested in an improved evidence base regarding polypharmacy for migraine prevention (i.e., what is the benefit of adding a second drug when patients are not effectively treated with one drug? Are drug side effects lessened when two drugs are used at lower dosages instead of one drug at a higher dose?).

Research Design Considerations

RCTs that compare the effectiveness of multi-drug combinations to single drug treatment are necessary to address this research need. The most important drug combinations to test are those commonly used in practice or those suggested in previously conducted open-label trials. The target population for such trials would be individuals who have failed treatment trials with several preventive medications. Again, blinding and sample size are key considerations. As with most of these research needs, subgroups will likely be a very important predictor of response and key subgroups relevant to this research question should be identified. Once identified, power calculations should be conducted to determine the necessary sample size to test differences between subgroups. Because subgroup analysis may be important and we are comparing two active treatments which may have a small marginal difference, the sample size necessary to address this research need will be large and therefore, resource requirements high. Table 9 provides specific details for consideration in funding and developing studies to address this research need.

Table 9. Episodic migraine: design considerations for fifth topical research need

Research Question: Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable?	
Considerations	RCT
Design Description	Individual patients randomly assigned to either combination preventive pharmacologic treatment or preventive pharmacologic treatment with a single drug and follow them over time to measure efficacy in preventing episodic migraine.
Population	Adults with episodic migraine that have previously failed preventive pharmacologic treatments with drugs from separate classes when used individually.
Intervention	Combination preventive pharmacologic treatment (e.g., tricyclic antidepressant + beta blocker).
Comparator	Preventive pharmacologic treatment with a single drug/placebo combination.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Studies of treatment duration of at least 6 months will provide the most clinically useful information.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is necessary to produce the valid results. Blinding is necessary to insure validity. Generalizability may be low.
Resource use, size and duration	High; large sample sizes to test differences among subgroups would provide most clinically meaningful information; likely necessary to recruit large samples and follow for significant length of time.
Ethical, legal, and social issues	Ethical challenges exist. However, both arms involve standard treatment that is non-invasive and harms are not typically life threatening.
Availability of data/ability to recruit	Fair, condition has fairly high prevalence.

Episodic Migraine: Sixth Topical Research Need

- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)

Disease characteristics among adults suffering from episodic migraine can vary widely.

Patients may have suffered from episodic migraine for as little as a few months to several years providing a wide range of chronicity. In addition to chronicity, other disease characteristics vary as well. Some individuals may suffer from an average of five headaches per month and others 15. The duration and severity of those headaches can also vary widely from individual to individual. Many of these characteristics are thought to influence patient response to preventive pharmacologic treatment. KQ 3 of the CER addressed the patient characteristics that influenced response to preventive medication. However, data was only available for a few condition-specific categories (e.g., migraine with aura, baseline migraine frequency) for certain medications. The Canadian Headache Society guidelines recommend preventive migraine medications specifically for patients with certain comorbidities (increased body mass index, hypertension, and depression/anxiety).⁴⁷ Our stakeholders agreed that an improved understanding of how disease characteristics modify treatment effectiveness would aid decisionmaking.

Research Design Considerations

While post hoc analyses of previous RCTs or cohort studies could be used to identify potential relationships between specific disease characteristics and response to treatment with particular drugs, a large RCT is the best approach to testing the hypothesized relationship. Most valuable would be to test relationships previously identified, but rated insufficient or low strength evidence, as well as relationships suspected based on observational studies or clinical practice. Power calculations will be critical to determine sample size with adequate subgroup populations necessary to test differences between groups. Specific research design considerations

are similar to other research needs and described in Table 10. If RCTs are not feasible, prospective cohort studies could be designed to enable larger samples, but investigators must take adequate steps to adjust for selection bias.

Table 10. Episodic migraine: design considerations for sixth topical research need

Research Question: Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to preventive pharmacologic treatments or placebo and followed over time.
Population	Adults with episodic migraine. A sample with diverse disease characteristics will be necessary.
Intervention	Preventive pharmacologic treatments.
Comparator	Placebo or active treatment.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Studies of treatment duration of at least 6 months will provide the most clinically useful information.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is necessary to produce the valid results. Blinding is necessary to insure validity. A large sample capable of testing these characteristics via subgroup differences is necessary. It will be necessary to perform power calculations to determine sufficient sample size within each a priori identified subgroup necessary to test differences. Overall sample size can then be approximated based upon distribution of disease characteristics in population. Generalizability will be enhanced by the recruitment of a diverse sample, but will be lower than cohort studies.
Resource use, size and duration	High; large sample sizes to test differences among subgroups is necessary and participants will likely need to be followed for several months.
Ethical, legal, and social issues	Ethical challenges exist. However, both arms involve standard treatment that is noninvasive, and harms are not typically life threatening.
Availability of data/ability to recruit	Fair, condition has fairly high prevalence. May be necessary to recruit patients from several headache clinics to insure adequate sample size within subgroups.

Chronic Migraine: First Topical Research Need

- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)

Fewer research questions rose to the top of the ranking process for chronic migraine prevention. While far fewer individuals suffer from chronic migraine than episodic migraine, the impact of the condition on their lives is substantially greater. Improved knowledge around these treatment-specific research needs could eventually lessen the disease burden among those suffering from chronic migraine.

This research need mirrors one aimed at the episodic migraine population. Enhanced knowledge on disease characteristics and response to treatment appears even more critical with regard to chronic than episodic migraine. However, data examining these relationships is even scarcer with regard to chronic migraine. The CER reported one trial that examined subgroup effects (prior topiramate use and medication overuse) of preventive treatment (topiramate vs. topiramate plus propranolol) in chronic migraine. Many other subgroups need to be analyzed to improve understanding of the influence of specific disease characteristics.

Research Design Considerations

Design issues for RCTs regarding preventive pharmacologic treatments for chronic migraine are essentially identical to those of episodic migraine for the corresponding research need, but have greater challenges. Conducting RCTs with chronic migraine populations will be more

difficult given the lower prevalence of the condition. Multi-site trials should be considered to recruit adequate sample sizes. Additionally, investigators might expect a greater degree of attrition among chronic migraine participants than among episodic migraine participants due to their poorer health status. Specific research design considerations are described in Table 11.

Table 11. Chronic migraine: design considerations for first topical research need

Research Question: Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to preventive pharmacologic treatments or placebo and followed over time.
Population	Adults with chronic migraine with diverse disease characteristics.
Intervention	Preventive pharmacologic treatments.
Comparator	Placebo.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Studies of treatment duration of at least 6 months will provide the most clinically useful information.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is necessary to produce the valid results. Blinding is necessary to insure validity. A large sample capable of testing these characteristics via subgroup differences is necessary. It will be necessary to perform power calculations to determine sufficient sample size within each a priori identified subgroup necessary to test differences. Overall sample size can then be approximated based upon distribution of disease characteristics in population. Generalizability will be enhanced by the recruitment of a diverse sample, but will be lower than cohort studies.
Resource use, size and duration	High; large sample sizes to test differences among subgroups is necessary and participants will likely need to be followed for several months.
Ethical, legal, and social issues	Ethical challenges exist. However, both arms involve standard treatment that is non-invasive and harms are not typically life threatening.
Availability of data/ability to recruit	Fair, condition has fairly high prevalence. May be necessary to recruit patients from several headache clinics to insure adequate sample size within subgroups.

Chronic Migraine: Second Topical Research Need

- What is the long-term (> 1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)

While this research question was not highly prioritized for episodic migraine, it is much more relevant for chronic migraine because these individuals often need preventive medications for long periods of time. This specific question was not addressed by the CER; however included trials had timelines much shorter than 1 year. If chronic migraine patients are expected to take preventive medications for years, we need an improved understanding of the long-term effectiveness and harms of these medications.

Research Design Considerations

For several reasons, an RCT is not likely feasible for this research need. Therefore, an alternative approach is to select a sample of adults maintaining the same preventive pharmacologic treatment for over one year and evaluate headache frequency and other outcomes at set intervals throughout their treatment. This design, interrupted time series (without a comparison group) is useful to identify trends in outcomes measures during a long course of treatment. Disadvantages include the limitations in the data available, as much of it will be obtained through the patient record and the potential inconsistencies in data collected over time and between providers. Table 12 provides more specific research design considerations for this research need.

Table 12. Chronic migraine: design considerations for second topical research need

Research Question: What is the long-term (> 1 year) effectiveness of preventive pharmacologic treatments for chronic migraine?	
Considerations	Interrupted Time Series (Without a Comparison Group)
Design Description	A group of individuals that have maintained a course of treatment for one year or more are selected. Outcomes at 1-year treatment duration are compared with outcomes achieved at other points in course of treatment.
Population	Adults with chronic migraine maintaining preventive treatment regimen for 1 year.
Intervention	Preventive pharmacologic treatment of 1-year duration.
Comparator	Preventive pharmacologic treatment of 3-, 6- and/or 9-months duration.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Short given that most data is historical.
Setting	Headache clinic data.
Advantages for Producing a Valid Result	Allows for study of unique intervention for rare condition and analysis of trends over time. Outcomes data at different time periods needs to be available in patient record. Results valid only for populations maintaining long-term treatment regimens. Analysis can generate hypothesis to be tested with experimental design.
Resource use, size and duration	Low, data from several headache clinics may be necessary to achieve adequate sample. Large sample that allows subgroup analysis would provide most useful information.
Ethical, legal, and social issues	Minimal, observational study.
Availability of data/ability to recruit	Rare condition and treatment may require coordination from several headache centers.

Chronic Migraine: Third Topical Research Need

- What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)

As with episodic migraine, the optimal duration of preventive pharmacologic treatment is now well understood. Improved understanding should result in improved prescribing behavior. As mentioned previously, scientific evidence does not inform decisions about the optimal treatment duration. This question is relevant for chronic as well as episodic migraine populations.

Research Design Considerations

RCTs are the best option for addressing this research need for reasons previously discussed. Recruiting and retaining sample populations will be especially challenging due to the duration of the intervention. This should be considered when calculating sample size. Additional research design considerations are described in Table 13.

Table 13. Chronic migraine: design considerations for third topical research need

Research Question: What is the optimal duration of preventive pharmacologic treatments for episodic migraine?	
Considerations	RCT
Design Description	Individual patients randomly assigned to preventive pharmacologic treatments of varying duration.
Population	Adults with chronic migraine.
Intervention	Active preventive pharmacologic treatment (e.g. topiramate) for 6, 9, or 12 months followed by placebo.
Comparator	Preventive pharmacologic treatment (e.g. topiramate) for 3 months followed by placebo.
Outcomes	Migraine frequency, quality of life, patient satisfaction, lost work days.
Timing	Outcomes measurement should extend through at least one-year from cessation of pharmacologic treatment; longer follow-up would be clinically valuable.
Setting	Headache clinic.
Advantages for Producing a Valid Result	This design is likely to produce the most valid results. Blinding is necessary to insure validity. Generalizability may be low.
Resource use, size and duration	Necessary to recruit large samples and follow for significant length of time; power calculation with planned subgroup analysis should be conducted to determine appropriate sample size.
Ethical, legal, and social issues	Ethical challenges are expected to be minimal. Harms related to long-term use of preventive pharmacologic treatments for migraine unclear; however most drugs used long term for other conditions.
Availability of data/ability to recruit	Fair. Condition is fairly prevalent and preventive pharmacologic treatments are standard care with harms that are not typically life threatening. Intervention requires significant time commitment from patients.

Discussion

This FRN project refined and prioritized research needs relevant to the KQs addressed in the draft CER Preventive Pharmacologic Treatments for Migraine released in April 2011.¹ We conducted a deliberative process to refine and expand research gaps identified in the CER through conversations with stakeholders who represented various perspectives of expertise on the topic. This process identified eight methodological and 22 topical research questions relevant to episodic and chronic migraine. We then asked stakeholders to prioritize research questions according to their potential impact. The highly ranked questions were deemed research needs. Stakeholders prioritized three methodological, six episodic migraine topical research questions, and three chronic migraine topical research needs.

Addressing methodological research needs will enhance the utility and comparability of future studies of migraine preventive pharmacologic treatments, specifically for chronic migraine. Identified episodic migraine topical research needs demonstrate the importance of an enhanced understanding the timing of preventive treatments and measuring effectiveness taking the full impact of treatments into account. Identifying biomarkers helpful in predicting response to preventive pharmacologic treatment is the third methodological research need.

Future studies evaluating preventive pharmacologic treatments for episodic and chronic migraine should by design attend closely to reducing bias as much as possible within randomized controlled trials. Double blinding is critical for this topic. Studies should be adequately powered to test hypothesized relationships, including among subgroups. Investigators should consult appropriate guidelines for controlled trials of migraine drugs.^{26,48}

We research design considerations that may assist sponsors and investigators in addressing these specific research needs; however, resources in the field provide more comprehensive guidance to conducting trials on the pharmacologic prevention of episodic and chronic migraine. The recent update of the Guidelines for Controlled Trials of Drugs in Migraine from the IHS Clinical Trials Subcommittee, extensively addresses ideal conduct of trials on preventative pharmacologic interventions specific to episodic migraine.⁴⁸ These guidelines discuss population selection, trial design, results, evaluation, and statistics. The Guidelines for Controlled Trials of Prophylactic Treatment of Chronic Migraine in Adults were published in 2008.²⁶ A third recently developed resource designed to guide comparative effectiveness research that is helpful to patients making health care decisions is the preliminary draft methodology report Our Questions, Our Decisions: Standards for Patient-Centered Outcomes Research from the Patient-Centered Outcomes Research Institute (PCORI).⁴⁹ Investigators addressing these research needs are urged to consult the relevant guidelines and reconcile guidelines with PCORI's standards for patient-centered outcomes research when designing studies.

While a strength of this project is the intended variety of perspectives brought by broad stakeholder participation, we were not able to collect a representative perspective from a larger sample of stakeholders. This is a major limitation. The stakeholders participating in this project were several experts on preventive pharmacologic treatments for episodic and chronic migraine. However, the prioritized research needs reflect the opinions of these stakeholders and may not be applicable to the broader population of stakeholders on this topic. Our stakeholder panel was also limited in size by standards and guidelines for statistical surveys administered by the Office of Management and Budget. These guidelines require compliance with the Paperwork Reduction Act and Information Collections Policy (44 USC 3501-3520).⁵⁰ The Act was designed to (1) minimize the paperwork burden on the public, (2) assure that high quality data are obtained, and (3) minimize costs. The Act requires special approval for projects that wish to include more than

nine nongovernment participants; however, the approval process exceeded the length of time available to complete this FRN project.

Finally, the finalization of the CER and related FRN project overlapped in time. This made stakeholder discussions challenging because stakeholders were provided with the draft CER Executive Summary that had not yet incorporated peer review comments. Many of these stakeholders were peer reviewers to the CER.

Future studies of preventive pharmacologic treatments for migraine in adults should seek to reduce bias as much as possible for the particular research design used. Literature examined for the draft CER provided adequate and consistent measurement and reporting of variables thought to confound or modify the effect of multidisciplinary rehabilitation programs, but because the ongoing CDE efforts appear to sufficiently address this concern, we did not include this methodological research question in our list prioritized by stakeholders.

Conclusions

This FRN project identified several research needs thought relevant by a select group of stakeholders to move the field forward:

- How should research of pharmacologic treatment for chronic migraine define treatment success?
- How should chronic migraine populations be defined in trials?
- What biomarkers help predict treatment response?
- What is the optimal duration of preventive pharmacologic treatments for episodic migraine? (T)
- If preventive drug treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels? (I, O)
- What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine? (O)
- What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine? (I)
- Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)
- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)
- Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)
- What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)
- What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)

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Abbreviations

ACE	Angiotensin converting enzyme
AHRQ	Agency for Healthcare Research and Quality
ARB	Angiotensin receptor blocker
CDE	Common Data Elements
CER	Comparative Effectiveness Review
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
FRN	Future Research Needs
ICHD-2	International Classification of Headache Disorders
IHS	International Headache Society
KQ	Key Question
NINDS	National Institute of Neurological Disorders and Stroke
PCORI	Patient-Centered Outcomes Research Institute
PICOTS	Population, intervention, comparison, outcome, timing, and setting
RCT	Randomized clinical trials
SF-36	Medical Outcome Study Short Form 36

Appendix A. Research Questions for Prioritization

Table A-1. Future Research Needs research questions for prioritization

Methodological Research Questions	
M1.	How should research of pharmacologic treatments for episodic migraine define treatment success?
M2.	How should research of pharmacologic treatment for chronic migraine define treatment success?
M3.	What is the minimal clinically important difference for the Migraine Disability Assessment questionnaire scores?
M4.	How should adverse effects be measured and reported in pharmacologic studies for the prevention of chronic and/or episodic migraine?
M5.	How should chronic migraine populations be defined in trials?
M6.	Should episodic and chronic migraine be treated as one progressive disease or as conditions arising from separate physiological mechanisms?
M7.	What biomarkers help predict treatment response?
M8.	What is the appropriate timing to evaluate treatment success or failure for each drug/class of drug for preventing chronic and/or episodic migraine?
Topical Questions: Episodic Migraine	
Benefits of Treatment	
E1.	What is the efficacy of angiotensin acting drugs (ACE inhibitors, angiotensin receptor blockers) in preventing episodic migraine? (I)
E2.	What is the efficacy of pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing episodic migraine? (O)
E3.	What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing episodic migraine? (I)
E4.	What is the efficacy of preventive pharmacologic treatments for episodic migraine combined with treatment of existing comorbidities? (P, I)
E5.	How does patient compliance with pharmacologic treatment for episodic migraine affect efficacy? (P)
E6.	What is the comparative effectiveness (head-to-head trials) of angiotensin acting drugs, beta blockers, and antiepileptics in preventing episodic migraine? (I, C)
E7.	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for episodic migraine in terms of validated measures of quality of life and migraine-related disability? (O)
E8.	What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for episodic migraine with regard to health care utilization (emergency department visits, hospitalizations, acute drug utilization, mental health visits, and medication overuse)? (O)
E9.	What is the dose-response relationship with regard to migraine occurrence and severity from preventive pharmacologic treatments for episodic migraine? (I, O)
E10.	What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for episodic migraine? (O)
E11.	What is the optimal duration of preventive pharmacologic treatments for episodic migraine? (T)
E12.	Are combinations of pharmacologic treatments effective in preventing episodic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)
E13.	If preventive drug treatment for episodic migraine is effective but discontinued, how likely is it that the episodic migraine will return to previous levels? (T)
E14.	What is the mechanism of action for drugs from each pharmacologic class used for episodic migraine prevention? (I)
E15.	Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for episodic migraine? (P)
Harms of Treatment	
E16.	What are the comparative harms (head-to-head trials) of angiotensin acting drugs, beta blockers, and approved antiepileptics for preventing episodic migraine? (I, C)
E17.	What is the dose response relationship with regard to harms from preventive pharmacologic treatments for episodic migraine? (I, O)
E18.	What is the long-term (>1 year) safety of preventive pharmacologic treatments for episodic migraine? (O)
Benefits/ Harms Patient Subgroups (Subgroups Identified: Comorbidities, Race/Ethnicity, Sex, Headache Frequency/Severity, Prior Treatment Failure Status)	
E19.	What is the efficacy of preventive pharmacologic treatments in preventing episodic migraine in patient subgroups? (P)
E20.	What is the comparative effectiveness (head-to-head trials) between angiotensin acting drugs, beta blockers, and approved antiepileptics for preventing episodic migraine in patient subgroups? (P)
E21.	What are the comparative harms (head-to-head trials) of angiotensin acting drugs, beta blockers, and approved

antiepileptics for preventing episodic migraine in patient subgroups? (P)

Topical Research Questions (PICOTS element): Chronic Migraine

Benefits of Treatment

- C1. What is the efficacy of angiotensin acting drugs (ACE inhibitors, angiotensin receptor blockers) in preventing chronic migraine? (I)
- C2. What is the efficacy of preventive pharmacologic treatments with respect to patient quality of life, migraine-related disability, and health care utilization in preventing chronic migraine? (O)
- C3. What is the efficacy of multimodal treatments (pharmacologic, behavioral, etc.) in preventing chronic migraine? (I)
- C4. What is the efficacy of pharmacologic treatments for chronic migraine combined with treatment of existing comorbidities? (P, I)
- C5. How does patient compliance with pharmacologic treatment for chronic migraine affect efficacy? (P)
- C6. What is the comparative effectiveness (head-to-head trials) of angiotensin acting drugs, beta blockers, and antiepileptics in preventing chronic migraine? (I, C)
- C7. What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for chronic migraine in terms of validated measures of quality of life and migraine-related disability? (O)
- C8. What is the comparative effectiveness (head-to-head trials) of preventive pharmacologic treatments for chronic migraine on health care utilization (emergency department visits, hospitalizations, acute drug utilization, mental health visits, and medication overuse)? (O)
- C9. What is the dose-response relationship with regard to migraine occurrence and severity from preventive pharmacologic treatments for chronic migraine? (I, O)
- C10. What is the long-term (>1 year) effectiveness of preventive pharmacologic treatments for chronic migraine? (O)
- C11. What is the optimal duration of preventive pharmacologic treatments for chronic migraine? (T)
- C12. Are combinations of pharmacologic treatments effective in preventing chronic migraine in patients for whom treatment with a single preventive drug has been either ineffective or intolerable? (I)
- C13. If preventive drug treatment for chronic migraine is effective but discontinued, how likely is it that chronic migraine will return to previous levels? (T)
- C14. What is the mechanism of action for drugs from each pharmacologic class used for chronic migraine prevention? (I)
- C15. Which disease characteristics (duration, severity, frequency of attacks, comorbidities) affect the efficacy of preventative pharmacologic treatments for chronic migraine? (P)

Harms of Treatment

- C16. What are the comparative harms (head-to-head trials) of angiotensin acting drugs and beta blockers and approved antiepileptics for preventing chronic migraine? (I, C)
- C17. What is the dose-response relationship with regard to harms from preventive pharmacologic treatments for chronic migraine? (I, O)
- C18. What is the long-term (>1 year) safety of preventive pharmacologic treatments for chronic migraine? (O)

Benefits/ Harms Patient Subgroups (Subgroups Identified: Comorbidities, Race/Ethnicity, Sex, Headache Frequency/Severity, Prior Treatment Failure Status)

- C19. What is the efficacy of preventive pharmacologic treatments in preventing chronic migraine in patient subgroups? (P)
- C20. What is the comparative effectiveness (head-to-head trials) of angiotensin acting drugs, beta blockers, and approved antiepileptics for preventing chronic migraine in patient subgroups? (P)
- C21. What are the comparative harms (head-to-head trials) of angiotensin acting drugs, beta blockers, and approved antiepileptics for preventing chronic migraine in patient subgroups? (P)

PICOTS = Population, intervention, comparison, outcome, timing, and setting.

Appendix B. Search Strategy for Ongoing Studies

Advanced Search for Intervention and Nonintervention Studies on www.ClinicalTrials.gov

Search Terms:

Prevent OR prevention OR prophylactic OR prophylaxis OR manage OR management

Condition:

Migraine

Age Group:

Adult and Senior

Appendix C. Ongoing Studies

NCT Number	Title	Keywords
NCT00285402	Efficacy and Safety Clinical Trial of Intranasal AST-726 for the Prevention of Migraine	New drug
NCT01090050	Treximet in the Treatment of Chronic Migraine	Combination drug Chronic migraine
NCT01513291	A Study of the Safety and Efficacy of MK-6096 for Migraine Prophylaxis in Participants With Episodic Migraine (MK-6096-020)	New drug Episodic migraine
NCT00055484	A Study to Measure the Safety and Effectiveness of Zonisamide in Subjects With Migraine Headache	Anti-epileptic
NCT00154063	Efficacy and Safety Study of E2007 in Migraine Prophylaxis	New drug
NCT00203216	A Clinical Study Examining the Safety and Effectiveness of a New Medication (Keppra®) for the Prevention of Migraine Headaches	New drug
NCT00210821	Comparing the Safety and Effectiveness of Topiramate With the Safety and Effectiveness of Amitriptyline in Preventing Migraine Headaches	Comparative effectiveness
NCT00210860	An Open Label Extension of a Study Comparing Topiramate and Amitriptyline in Migraine Prevention.	long-term safety and effectiveness
NCT00210873	An Open Label Extension of a Study of Topiramate in Chronic Migraine.	long-term safety and effectiveness chronic migraine
NCT00216606	The Effectiveness and Safety of Topiramate on Prevention of Chronic Migraine	Chronic migraine
NCT00216619	The Prolonged Use of Topiramate for Preventing Migraine Headaches	long-term safety and effectiveness
NCT00242866	Use Of GW274150 In The Prophylactic Treatment Of Migraine	New drug
NCT00297336	An Observational Study Evaluating the Safety of Topiramate for the Prevention of Migraine	Safety
NCT00301665	Efficacy and Safety Study of Dysport® Used for Migraine Prophylaxis	OnabotulinumtoxinA
NCT00311662	Efficacy and Tolerability of Tonabersat in the Prophylaxis of Migraine Headache	Tonabersat
NCT00334178	Evaluation of the Efficacy and Safety of Laxymig® as Prophylactic Treatment in Patients With Migraine	Anti-epileptic
NCT00440518	A Study Designed to Test the Effectiveness and Safety of Treating Patients With Lacosamide for Migraine Prophylaxis	Anti-epileptic
NCT00534560	Dose Ranging Study of the Efficacy and Tolerability of Tonabersat in the Prophylaxis of Migraine Headache	Tonabersat
NCT00742209	Prevention Study in Adult Patients Suffering From Migraine Headaches	New drug Dose-reponse Episodic migraine
NCT00772031	NINDS CRC Chronic Migraine Treatment Trial	topiramate and propranolol combined treatment chronic migraine
NCT01060111	Adequate Therapy of Topiramate in Migraine	topiramate and propranolol combined treatment

		episodic migraine
NCT01146509	An Evaluation Of The Efficacy And Safety Of Donepezil Hydrochloride (E2020) In Migraine Prophylaxis	donepezil hydrochloride
NCT01402479	An Open-labeled Trial of Ramipril in Patients With Migraine	Ramipril ACE inhibitor Chronic migraine
NCT01319825	Preventive Treatment of Episodic and Chronic Migraine	Milnacipran Antidepressant Episodic migraine Chronic migraine
NCT00443352	A Research Study Examining The Use Of Duloxetine In The Prevention Of Migraine Headache	Duloxetine Antidepressant Episodic migraine
NCT00884663	Candesartan Versus Propranolol for Migraine Prevention	Comparative effectiveness Candesartan (ARB) Propranolol Chronic migraine Episodic migraine
NCT01122381	Comparison of a Drug and Placebo in the Prevention of Migraine Headaches	Ethosuximide Episodic migraine
NCT01151787	Efficacy and Safety of Cyclobenzaprine Hydrochloride Extended Release for the Treatment of Chronic Migraine	cyclobenzaprine hydrochloride chronic migraine
NCT01225263	Statin/Vitamin D & Migraine Study	Simvastatin statin Episodic migraine
NCT01357031	Study With Amitriptylin to Evaluate the Efficacy of Melatonin in Treatment of Migraine	Amitriptylin Episodic migraine
NCT01432379	BOTOX® Prophylaxis in Patients With Chronic Migraine	OnabotulinumtoxinA Chronic migraine
NCT01516892	A Long-term Efficacy, Safety, and Tolerability Study of BOTOX® in Patients With Chronic Migraine	OnabotulinumtoxinA Chronic migraine