Effective Health Care

Drugs and Devices to Prevent Migraines in Adults

Results of Topic Selection Process & Next Steps

The nominator is interested in an update to a 2013 AHRQ evidence review on preventative pharmacology for migraines in adults. The nominator is concerned with the currency of the information presented in the archived review, and believes an update would inform the public about new preventative treatments for migraines in adults. Due to limited program resources, the Effective Health Care (EHC) program will not develop a review at this time. No further activity on this topic will be undertaken by the EHC Program.

Topic Brief

Topic Name: Drugs and Devices to Prevent Migraines in Adults

Topic #: 0703

Nomination Date: September 14, 2016

Topic Brief Date: March 2017

Authors
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Conflict of Interest: None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

Summary of Key Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: While specific interventions on the prevention of migraines have been well reviewed, there is no recent comprehensive review, and a new AHRQ evidence review would therefore not be duplicative.
    - The Canadian Headache Society performed a high quality systematic review and published a guideline on migraine prophylaxis, which included subgroup analyses on pregnant women and comorbidities. This review was published in 2012 but the search dates are more recent than those of the 2013 AHRQ review. Five separate Cochrane reviews examined SSRI/SNRIs; gabapentin and pregabalin; Valproate; topiramate; and anticonvulsants other than the aforementioned anticonvulsants for prevention of episodic and chronic migraine.
    - We identified a Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review, a health technology assessment, and a Cochrane protocol examining onabotulinumtoxin A for chronic migraine. The CADTH review included subgroup analyses on age and race/ethnicity. A protocol registered in PROSPERO describes plans to examine a wide variety of pharmacologic and non-

pharmacological interventions for episodic and chronic migraine, with a subgroup analysis on age.
    - We identified no reviews examining pharmacologic + non-pharmacological vs pharmacologic interventions for prevention of migraines in adults (KQ 1d), harms of approaches to drug management (KQ 2c), or subgroup analysis for individuals on concomitant medications (KQ 3e).
    - While not systematic reviews, the nominator may be interested in two February 2017 publications from The Medical Letter on Drugs and Therapeutics—a physician-targeted column and comparison chart of 18 drugs and doses, one device, and Botox for the prevention of migraines
- Impact: The nomination has high impact potential due to the lack of current guidance on effective preventative pharmacology and devices for migraines. Current guidelines are at least four years old, and two new devices (Cefaly and CerenaTMS) have been FDA approved since that time.
- Feasibility: An AHRQ evidence review is feasible at this time.
    - *Size/scope of review:* Our search of PubMed for pharmacologic prophylaxis for migraines resulted in 366 unique titles. Upon title and abstract review of all 366 results, we identified a total of 40 studies potentially relevant to the key questions in the nomination. Our search of PubMed for device prophylaxis for migraines resulted in 18 search results. Upon title and abstract review of all 18 results, we identified 3 studies potentially relevant to the key questions in the nomination. In total, 43 relevant studies were identified. Studies were found for all key questions, except KQ 4e, examining drug/device effectiveness in subgroups using concomitant medications.
    - *Clinicaltrials.gov:* We identified 40 clinical trials, studying pharmacological interventions and devices to prevent migraines. We found clinical trials for all key questions except KQs 4a (age), 4c (race/ethnicity), 4d (comorbidities), and 4e (concomitant medications). These four questions are all subgroup analysis questions, and none of the identified clinical trials described intent to examine results by these specific subgroups.
- Value: The nomination has a high value potential, given that the American Academy of Neurology and the American Headache Society plan to work together to use a new AHRQ systematic review to update their 2012 joint guidelines.

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Introduction

Approximately 38 million men, women, and children in the United States suffer from one of the many forms of migraines. While there are dozens of drugs approved to treat migraines, there are only four medications for migraine prevention that are both FDA-approved and available in the United States: propranaolol, timolol, divalproex sodium, and topiramate.[1] There are many classes of drugs commonly used off-label for the prevention of migraines, including beta-blockers, antidepressants, anticonvulsants, and NSAIDs among others.[1]

Topic nomination #0703 was received on September 14, 2016. This nomination was submitted by a researcher from the Urban Institute. After engaging with the American Academy of Neurology (AAN), the AAN and the American Headache Society (AHS) agreed to partner with AHRQ to use a systematic review to update their guidelines. The key questions and PICOTs (population, interventions, comparators, outcomes, and timing) were updated to include benefits and harms of additional drugs and introduced devices to prevent migraines. The key questions for this nomination are:

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

a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment?
b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?
c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments?
d. How do preventive pharmacological treatments combined with nondrug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone?
e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes?

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

a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?
b. What are the harms from preventive pharmacologic treatments when compared to active 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. What are the benefits and harms of devices intended to prevent migraine attacks in adults?

Key Question 4. Does effectiveness of pharmacological treatments or devices for preventing migraines in adults vary by patient characteristics?

a. Age
b. Pregnancy
c. Race/Ethnicity
d. Comorbidities
e. Concomitant Medications

To define the inclusion criteria for the key questions we specify the population, interventions, comparators, and outcomes of interest. See Table 1.

Table 1. Key Question and PICOs

Key Questions	1. What are the efficacy and comparative effectiveness of pharmacological treatments for preventing migraine attacks in adults? a. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to placebo or no active treatment? b. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments? c. How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active nonpharmacological treatments? d. How do preventive pharmacological treatments combined with non-drug treatments affect patient-centered and intermediate outcomes when compared to pharmacological treatments alone? e. How might dosing regimens or duration of treatments influence the effects of the treatments on patient-centered outcomes? How might approaches to drug management (such as patient	2. What are the comparative harms from pharmacological treatments for preventing migraine attacks in adults? a. What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment? b. What are the harms from preventive pharmacologic treatments when compared to active 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?	3. What are the benefits and harms of devices intended to prevent migraine attacks in adults?	4. Does effectiveness of pharmacological treatments or devices for preventing migraines in adults vary by patient characteristics? a. Age b. Pregnancy c. Race/Ethnicity d. Comorbidities e. Concomitant Medications

	care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring) influence results?			
Populations	Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society	Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society	Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society	Adults with episodic migraine, chronic daily headache, or chronic migraine as defined by the Headache Classification Subcommittee of the International Headache Society, and any of the following patient characteristics: • Age • Pregnancy • Race and ethnicity • Comorbidities (depression, bipolar disorder, anxiety, diabetes, hypertension, cardiovascular diseases, others) • Concomitant medications for comorbid conditions
Interventions	• Drugs approved by the FDA (such as propranolol, timolol, topiramate, and divalproex sodium) to prevent episodic migraine and to treat chronic migraine (such as Botox). • Off-label medications available in the United States and previously examined in clinical trials for preventing migraine • Monotherapy. • Multidrug interventions. • Combined pharmacological with nonpharmacological modalities: behavioral interventions with education,	• Drugs approved by the FDA (such as propranolol, timolol, topiramate, and divalproex sodium) to prevent episodic migraine and to treat chronic migraine (such as Botox). • Off-label medications available in the United States and previously examined in clinical trials for preventing migraine • Monotherapy. • Multidrug interventions. • Combined pharmacological with nonpharmacological modalities: behavioral interventions with education,	Devices approved by the FDA to prevent episodic and chronic migraines, including but not limited to: transcutaneous facial nerve stimulation, transmagnetic stimulation, and vagal nerve stimulation	N/A

	exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements. • Disease management programs including, but not limited to, patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring	exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, and dietary supplements. • Disease management programs including, but not limited to, patient care teams, integrated care, coordinated care, patient education, drug surveillance, or interactive drug monitoring		
Comparators	• Placebo. • Drug treatments (comparative effectiveness). • Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, dietary supplements, and TENS therapy.	• Placebo. • Drug treatments (comparative effectiveness). • Nonpharmacological treatments: behavioral interventions with education, exercise, biofeedback, relaxation techniques, yoga, massage, acupuncture, dietary supplements, and TENS therapy.	Placebo, other FDA approved active device	N/A
Outcomes	Patient-centered outcomes: • Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review. • Quality of life. • Patient satisfaction. • Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes. • Emergency visits, loss of work or school days; treatment failure. Intermediate outcomes: • Number of headache days.	Patient-centered outcomes: • Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review. • Quality of life. • Patient satisfaction. • Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes. • Emergency visits, loss of work or school days; treatment failure. Intermediate outcomes: • Number of headache days.	Patient-centered outcomes: • Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review. • Quality of life. • Patient satisfaction. • Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes. • Emergency visits, loss of work or school days; treatment failure. Intermediate outcomes: • Number of headache days.	Patient-centered outcomes: • Reduction of migraine attacks by >50 percent from baseline; primary outcome for the review. • Quality of life. • Patient satisfaction. • Composite patient centered outcomes defined as an aggregate improvement of the aforementioned outcomes. • Emergency visits, loss of work or school days; treatment failure. Intermediate outcomes: • Number of headache days.

	• Number of moderate to severe headache days. • Improvement in associated symptoms. • Use of drugs for acute migraine (prescribed or over-counter). • Physician/healthcare professional (HCP) visits. Harms: • All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness). • Treatment discontinuation due to adverse effects. • Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).	• Number of moderate to severe headache days. • Improvement in associated symptoms. • Use of drugs for acute migraine (prescribed or over-counter). • Physician/healthcare professional (HCP) visits. Harms: • All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness). • Treatment discontinuation due to adverse effects. • Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).	• Number of moderate to severe headache days. • Improvement in associated symptoms. • Use of drugs for acute migraine (prescribed or over-counter). • Physician/healthcare professional (HCP) visits. Harms: • All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness). • Treatment discontinuation due to adverse effects. • Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).	• Number of moderate to severe headache days. • Improvement in associated symptoms. • Use of drugs for acute migraine (prescribed or over-counter). • Physician/healthcare professional (HCP) visits. Harms: • All reported adverse reactions and effects (such as anxiety, nausea, vomiting, sleep time reduction, drowsiness, or weakness). • Treatment discontinuation due to adverse effects. • Additional medical resource utilization to manage adverse effects (e.g., prescription medication, urgent care/emergency services, physician/HCP visits).
Timing	6 months or more	Any time	Any time	Any time

Methods

To assess topic nomination *#0703 Drugs and Devices to Prevent Migraines in Adults* for priority for a systematic review or other AHRQ EHC report, we used a modified process based on established criteria. Our assessment is hierarchical in nature, with the findings of each step in our assessment determining the need for further evaluation of the next step. Details related to our assessment are provided in Appendix A.

1. Determine the *appropriateness* of the nominated topic for inclusion in the EHC program.
2. Establish the overall *importance* of a potential topic as representing a health or healthcare issue in the United States.
3. Determine the *desirability of new evidence review* by examining whether a new systematic review or other AHRQ product would be duplicative.
4. Assess the *potential impact* a new systematic review or other AHRQ product.
5. Assess whether the *current state of the evidence* allows for a systematic review or other AHRQ product (feasibility).
6. Determine the *potential value* of a new systematic review or other AHRQ product.

Appropriateness and Importance

We assessed the nomination for appropriateness and importance (see Appendix A).

Desirability of New Review/Duplication

We searched for high-quality, completed or in-process evidence reviews pertaining to the key questions of the nomination. Table 2 includes the citations for the reviews that were determined to address the key questions.

Impact of a New Evidence Review

The impact of a new evidence review was assessed by analyzing the current standard of care, the existence of potential knowledge gaps, and practice variation. We considered whether a new review could influence the current state of practice through various dissemination pathways (practice recommendation, clinical guidelines, etc.).

Feasibility of a New Evidence Review

We conducted two literature searches in PubMed from October 2011 to March 2017 (Appendix B). One search focused on prophylactic drugs, and one search focused on prophylactic devices. Because a small number of articles were identified, we reviewed all titles and abstracts for inclusion and classified identified studies by study design, to assess the size and scope of a potential evidence review. See *Table 2, Feasibility Column, Size/Scope of Review Section* for the citations of included studies.

Value

We assessed the nomination for value (see Appendix A). We considered whether a partner organization could use the information from the proposed evidence review to facilitate evidence-based change; or the presence of clinical, consumer, or policymaking context that is amenable to evidence-based change.

Compilation of Findings

We constructed a table outlining the selection criteria as they pertain to this nomination (see Appendix A).

Results

Appropriateness and Importance

This is an appropriate and important topic. Roughly 38 million people in the United States suffer from migraines, 2-3 million of which are categorized as chronic.[2] Prophylaxis and treatment of migraines represent a significant cost for a large proportion of the US population.

Desirability of New Review/Duplication

While specific interventions on the prevention of migraines have been well reviewed, there exists no recent comprehensive review, and a new AHRQ evidence review would therefore not be duplicative.

The Canadian Headache Society performed a high quality systematic review[3] and published a guideline on migraine prophylaxis, which included subgroup analyses on pregnant women and comorbidities, but was done before the 2013 AHRQ review[4] was published. We identified five Cochrane reviews[5-9] examining SSRI/SNRIs[5] (vs placebo, head-to-head, and harms); gabapentin and pregabalin[6] (vs placebo, head-to-head, dosing/duration, and harms); Valproate[7] (vs placebo, head-to-head, vs non-pharmacologic interventions, and harms); topiramate[9] (vs placebo, head-to-head, dosing/duration, and harms); and anticonvulsants other than the aforementioned[8] (vs placebo, head-to-head, dosing/duration, and harms) for prevention of episodic and chronic migraine. We also identified a CADTH systematic review,[10] a health technology assessment,[11] and a Cochrane protocol[12] examining onabotulinumtoxinA as treatment for chronic migraine. The CADTH review[10] includes subgroup analyses on age and race/ethnicity. A PROSPERO protocol plans to examine a wide variety of pharmacologic and non-pharmacological interventions for episodic and chronic migraine, with a subgroup analysis on age.[13]

We identified no reviews examining pharmacologic + non-pharmacological vs pharmacologic interventions for prevention of migraines in adults (KQ 1d), harms of approaches to drug management (KQ 2c), or subgroup analysis for individuals on concomitant medications (KQ 3e).

While not systematic reviews, of potential interest to the nominator are two February 2017 publications from The Medical Letter on Drugs and Therapeutics—a physician-targeted column[14] and comparison chart[15] of 18 drugs and doses, one device, and Botox for the prevention of migraines. This comparison chart includes information on dosing, efficacy, precautions, indications for pregnancy, other comments, and cost.

Impact of a New Evidence Review

The impact of a new review would be high. The standard of care is unclear. The previous guidelines are out-of-date, as there are drugs and devices for the prevention of migraines that have been FDA approved since the search dates of the previous AHRQ and CADTH reviews, and AAN/AHS guidelines (Cefaly and CerenaTMS). Additionally, there is practice variation due to the number of prevention options available, and lack of current guidelines directing practice.

Feasibility of a New Evidence Review

An AHRQ systematic review on the topic is feasible at this time. Two PubMed searches (one searching for drugs and one searching for devices) resulted in a total of 384 results. Upon title and abstract review of all results, 43 were found to be potentially relevant across key questions. 28 different preventative drugs, three devices, and acupuncture are represented in these 43

published studies. Two searches of ClinicalTrials.gov, one searching for drugs and one searching for devices, resulted in 40 relevant trials that have been completed in the last two years or are projected to be completed in the next two years.

34 of the identified studies examine 28 different prophylactic pharmacologic therapies such as topiramate, amitriptyline, and gabapentin. Four studies examine Onabotulinumtoxin A (trade name: Botox) and its efficacy in preventing migraines.[16-19] Three studies examine the following three devices: supraorbital transcutaneous stimulator,[20] trigeminal nerve stimulation (trade name: Cefaly),[21] and non-invasive vagus nerve stimulator.[22] Additionally, two studies examined the efficacy of acupuncture versus pharmacologic prevention of migraines.[23,24] See *Table 2, Feasibility* column for the citations that were determined to address the key questions.

Table 2. Key question with the identified corresponding evidence reviews and original research

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
1a: Pharmacologic vs placebo/no active treatment	Total number of completed or in-process evidence reviews: 14 • Cochrane: 5[5-9] • Other: 4[3,10,25,26] • HTA: 1[11] • Cochrane Protocol: 1[12] • Other Protocol: 3[13,27,28]	Size/scope of review Relevant Studies: 13 • RCT: 9[16-18,29-34] • Prospective: 1[19] • Longitudinal Trends Analysis: 1[35] • Post Hoc Analysis: 2[36,37] ClinicalTrials.Gov Relevant studies: 10 • Recruiting: 5[38-42] • Active, not recruiting: 4[43-46] • Complete: 1[47]
1b: Pharmacologic vs pharmacologic	Total number of completed or in-process evidence reviews: 10 • Cochrane: 5[5-9] • Cochrane Protocol: 1[12] • Other: 1[26] • Other Protocol: 2[13,28]	Size/scope of review Relevant Studies: 17 • RCT: 12[16,30,31,34,47-54] • Randomized Open-Label:1[55] • Longitudinal: 1[35] • Retrospective: 1[56] • Post Hoc Analysis: 1[57] ClinicalTrials.Gov Relevant studies: 5 • Recruiting: 1[41] • Active, not recruiting: 2[58,59] • Complete: 2[40,60]
1c: Pharmacologic vs. non-pharmacologic	Total number of completed or in-process evidence reviews: 8 • Cochrane: 1[7] • Other Protocol: 1[13]	Size/scope of review Relevant Studies: 3 • RCT: 1[24] • Prospective: 1[23] • Longitudinal: 1[35] ClinicalTrials.Gov Relevant studies: 1 • Recruiting: 1[41]
1d: Pharmacologic + non-pharmacologic vs pharmacologic	None identified.	Size/scope of review Relevant Studies: 1 • Longitudinal: 1[35]

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
		ClinicalTrials.Gov Relevant studies: 1 • Recruiting: 1[41]
1e: Dosing, duration and approaches to drug management	Total number of completed or in-process evidence reviews: 8 • Cochrane: 4[6-9] • Other: 2[3,25] • Cochrane Protocol: 1[12] • Other Protocol: 1[27]	Size/scope of review Relevant Studies: 15 • RCT: 3[17,48,61] • Prospective: 1[62] • Cross-Sectional: 1[63] • Open-Label: 1[64] • Longitudinal: 1[35] • Observational: 3[65-67] • Retrospective: 3[68-70] • Post Hoc: 2[36,57] ClinicalTrials.Gov Relevant studies: 6 • Not yet recruiting: 1[71] • Recruiting: 2[72,73] • Active, not recruiting: 2[74,75] • Complete: 1[60]
2a: Harms of pharmacologic vs. placebo/no active treatment	Total number of completed or in-process evidence reviews: 8 • Cochrane: 5[5-9] • Other: 2[26,76] • Other Protocol: 1[27]	Size/scope of review Relevant Studies Identified: 6 • RCT: 5[17,31-34] • Post Hoc Analysis: 1[36] ClinicalTrials.Gov Relevant studies: 22 • Recruiting: 11[39-41,43,44,72,73,77-80] • Active, not recruiting: 7[2,78-83] • Complete: 4[47,71,75,84]
2b: Harms of pharmacologic vs pharmacologic	Total number of completed or in-process evidence reviews: 3 • Cochrane: 1[5] • Other: 2[26,76]	Size/scope of review Relevant Studies: 12 • RCTs: 8[31,34,48,50-54] • Randomized, Open-Label: 1[55] • Retrospective: 1[56] • Post Hoc Analysis: 2[57] ClinicalTrials.Gov Relevant studies: 5 • Recruiting: 1[41] • Active, not recruiting: 2[58,85] • Complete: 2[41,47]
2c: Harms of approaches to drug management	None identified.	Size/scope of review Relevant Studies: 9 • Prospective: 1[62] • Cross-Sectional: 1[63] • Observational: 3[65-67] • Longitudinal: 1[35] • Retrospective: 1[68] ClinicalTrials.Gov Relevant studies: 1

Key Question	Duplication (Completed or In-Process Evidence Reviews)	Feasibility (Published and Ongoing Research)
		• Active, not recruiting: 1[74]
3: Devices	None identified.	Size/scope of review Relevant Studies: 3 • RCT: 1[20] • Prospective: 1[21] • Prospective Observational: 1[22] ClinicalTrials.Gov Relevant studies: 11 • Recruiting: 6[2,10,82,86-88] • Complete: 5[39,83,89-91]
4a: Variation in effectiveness—age	Total number of completed or in-process systematic reviews: 4 • Other: 2[10,25] • Other Protocol: 2[13,27]	Size/scope of review Relevant Studies: 2 • Retrospective: 1[69] • Post Hoc Analysis: 1[92] Clinical trials None identified.
4b: Variation in effectiveness—pregnancy	Total number of completed or in-process evidence reviews: 1 • Other: 1[3]	Size/scope of review Relevant Studies: 2 • Post Hoc Analysis: 2[93,94] Clinical trials Relevant studies: 1 • Complete: 1[95]
4c: Variation in effectiveness—race/ethnicity	Total number of completed or in-process evidence reviews: 1 • Other: 1[10]	Size/scope of review Relevant Studies: 1 • Post Hoc Analysis: 1[92] Clinical trials None identified.
4d: Variation in effectiveness—comorbidities	Total number of completed or in-process evidence reviews: 1 • Other: 1[3]	Size/scope of review Relevant Studies: 5 • RCT: 1[54] • Prospective: 2[19,62] • Open-Label: 1[96] • Post Hoc Analysis: 1[92] Clinical trials None identified.
4e: Variation in effectiveness—concomitant medications	None identified.	Size/scope of review None identified. Clinical trials None identified.

Abbreviations: HTA=Health Technology Assessment; RCT=Randomized Controlled Trial

Value

The nomination has a high value potential, given that the AAN/AHS will work together to use a new AHRQ systematic review to update their 2012 joint guidelines.

Summary of Findings

- Appropriateness and importance: The nomination is both appropriate and important.
- Duplication: While specific interventions on the prevention of migraines have been well reviewed, there is no recent comprehensive review, and a new AHRQ evidence review would therefore not be duplicative.
    - The Canadian Headache Society performed a high quality systematic review and published a guideline on migraine prophylaxis, which included subgroup analyses on pregnant women and comorbidities. This review was published in 2012 but the search dates are more recent than those of the 2013 AHRQ review. Five separate Cochrane reviews examined SSRI/SNRIs; gabapentin and pregabalin; Valproate; topiramate; and anticonvulsants other than the aforementioned anticonvulsants for prevention of episodic and chronic migraine.
    - We identified a Canadian Agency for Drugs and Technologies in Health (CADTH) systematic review, a health technology assessment, and a Cochrane protocol examining onabotulinumtoxin A for chronic migraine. The CADTH review included subgroup analyses on age and race/ethnicity. A protocol registered in PROSPERO describes plans to examine a wide variety of pharmacologic and non-pharmacological interventions for episodic and chronic migraine, with a subgroup analysis on age.
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    - While not systematic reviews, the nominator may be interested in two February 2017 publications from The Medical Letter on Drugs and Therapeutics—a physician-targeted column and comparison chart of 18 drugs and doses, one device, and Botox for the prevention of migraines
- Impact: The nomination has high impact potential due to the lack of current guidance on effective preventative pharmacology and devices for migraines. Current guidelines are at least four years old, and two new devices (Cefaly and CerenaTMS) have been FDA approved since that time.
- Feasibility: An AHRQ evidence review is feasible at this time.
    - *Size/scope of review:* Our search of PubMed for pharmacologic prophylaxis for migraines resulted in 366 unique titles. Upon title and abstract review of all 366 results, we identified a total of 40 studies potentially relevant to the key questions in the nomination. Our search of PubMed for device prophylaxis for migraines resulted in 18 search results. Upon title and abstract review of all 18 results, we identified 3 studies potentially relevant to the key questions in the nomination. In total, 43 relevant studies were identified. Studies were found for all key questions, except KQ 4e, examining drug/device effectiveness in subgroups using concomitant medications.
    - *Clinicaltrials.gov:* We identified 40 clinical trials, studying pharmacological interventions and devices to prevent migraines. We found clinical trials for all key questions except KQs 4a (age), 4c (race/ethnicity), 4d (comorbidities), and 4e (concomitant medications). These four questions are all subgroup analysis questions, and none of the identified clinical trials described intent to examine results by these specific subgroups.
- Value: The nomination has a high value potential, given that the AAN/AHS will work together to use a new AHRQ systematic review to update their 2012 joint guidelines.

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Appendices

Appendix A: Selection Criteria Summary Appendix

B: Search Strategy & Results (Feasibility)

Appendix A. Selection Criteria Summary

Selection Criteria	Supporting Data
1. Appropriateness	
1a. Does the nomination represent a health care drug, intervention, device, technology, or health care system/setting available (or soon to be available) in the U.S.?	Yes, this topic represents health care drugs and interventions available in the U.S.
1b. Is the nomination a request for a systematic review?	Yes, this topic is a request for an update for an AHRQ 2013 systematic review on preventative pharmacology for migraine in adults.
1c. Is the focus on effectiveness or comparative effectiveness?	Yes, the focus of this nomination is on both effectiveness and comparative effectiveness.
1d. Is the nomination focus supported by a logic model or biologic plausibility? Is it consistent or coherent with what is known about the topic?	Yes, it is biologically plausible. Yes, it is consistent with what is known about the topic.
2. Importance	
2a. Represents a significant disease burden; large proportion of the population	Yes, this topic represents a significant burden. Roughly 38 million people in the United States suffer from migraines, 2-3 million of which are categorized as chronic.[2]
2b. Is of high public interest; affects health care decision making, outcomes, or costs for a large proportion of the US population or for a vulnerable population	Yes, this topic affects heath care decisions for a large, vulnerable population. Prophylaxis and treatment of migraines represents a significant cost for a large proportion of the US population.
2c. Represents important uncertainty for decision makers	Yes, this topic represents important uncertainty for decision makers. There are dozens of approved and off-label drugs and devices to prevent migraines, and very little current guidance regarding what to use.
2d. Incorporates issues around both clinical benefits and potential clinical harms	Yes, this nomination addresses both benefits and potential harms of preventing of migraines.
2e. Represents high costs due to common use, high unit costs, or high associated costs to consumers, to patients, to health care systems, or to payers	Yes, this nomination represents a condition that may results in high costs due for consumers and payers.
3. Desirability of a New Evidence Review/Duplication	
3. Would not be redundant (i.e., the proposed topic is not already covered by available or soon-to-be available high-quality systematic review by AHRQ or others)	While specific interventions on the prevention of migraines have been well reviewed, there exists no recent comprehensive review, and a new AHRQ evidence review would therefore not be duplicative. The Canadian Headache Society performed a high quality systematic review and published a guideline on migraine prophylaxis, which included subgroup analyses on pregnant women and comorbidities, but was done before the 2013 AHRQ review was published. We identified five Cochrane reviews examining SSRI/SNRIs (vs placebo, head-to-head, and harms); gabapentin and pregabalin (vs placebo, head-to-head, dosing/duration, and harms); Valproate (vs placebo, head-to-head, vs non-pharmacologic interventions, and harms); topiramate (vs placebo, head-to-head, dosing/duration, and harms); and anticonvulsants other than the aforementioned (vs

	placebo, head-to-head, dosing/duration, and harms) for prevention of episodic and chronic migraine. We also identified a CADTH systematic review, a health technology assessment, and a Cochrane protocol examining onabotulinumtoxinA as treatment for chronic migraine. The CADTH review includes subgroup analyses on age and race/ethnicity. A PROSPOERO protocol plans to examine a wide variety of pharmacologic and non-pharmacological interventions for episodic and chronic migraine, with a subgroup analysis on age. We identified no reviews examining pharmacologic + non-pharmacological vs pharmacologic interventions for prevention of migraines in adults (KQ 1d), harms of approaches to drug management (KQ 2c), or subgroup analysis for individuals on concomitant medications (KQ 3e).
4. Impact of a New Evidence Review	
4a. Is the standard of care unclear (guidelines not available or guidelines inconsistent, indicating an information gap that may be addressed by a new evidence review)?	Yes, the standard of care is unclear. The previous guidelines are out-of-date, as there are drugs and devices for the prevention of migraines that have been FDA approved since the search dates of the previous AHRQ and CADTH reviews, and AAN/AHS guidelines.
4b. Is there practice variation (guideline inconsistent with current practice, indicating a potential implementation gap and not best addressed by a new evidence review)?	Yes, there is practice variation due to the number of prevention options available, and lack of current guidelines.
5. Primary Research	
5. Effectively utilizes existing research and knowledge by considering: - Adequacy (type and volume) of research for conducting a systematic review - Newly available evidence (particularly for updates or new technologies)	An AHRQ systematic review on the topic is feasible at this time. Two PubMed searches resulted in a total of 384 results. Upon title and abstract review of all results, 43 were found to be potentially relevant across key questions. 28 different preventative drugs, three devices, and acupuncture are represented in these 43 published studies. Two searches of ClinicalTrials.gov resulted in 40 relevant trials that have been completed in the last two years or are projected to be completed in the next two years.
6. Value	
6a. The proposed topic exists within a clinical, consumer, or policy-making context that is amenable to evidence-based change	Yes, this nomination exists within a clinical, consumer, and policy-making context. A review on this topic would inform the update of AAN/AHS guidelines as well as impact clinical decision-making to optimize benefits of treatment while reducing potential harms. Consumers will be able to use the results of an AHRQ systematic review to decide which preventative pharmacology or device may be most appropriate for their migraines.
6b. Identified partner who will use the systematic review to influence practice (such as a guideline or recommendation)	Yes, the AAN/AHS have partnered and will update their evidence-based guidelines based on the results of an AHRQ evidence review.

Abbreviations: AAN=American Association of Neurology; AHRQ=Agency for Healthcare Research and Quality; AHS=American Headache Society

Appendix B. Search Strategy & Results (Feasibility)

Drug Search

Topic: Drug therapy for the prevention of Migraine Date: October 4, 2016	Database Searched: MEDLINE (PubMed)
Concept	**Search String**
Migraine	("Migraine Disorders"[Mesh]) OR migraine[Title/Abstract]
AND	
Prevention Prophylactic Prophylaxis Preventive Prevent Preventative	(("Primary Prevention"[Mesh] OR "prevention and control" [Subheading])) OR ((prevention[Title/Abstract] OR prophylactic[Title/Abstract] OR prophylaxis[Title/Abstract] OR preventive[Title/Abstract] OR prevent[Title/Abstract] OR preventative[Title/Abstract]))
AND	
Drug therapy: "brain-derived neurotrophic factor" 5-HT* Alpha-T angoinsts Amitriptyline Amoxapine Anticonvulsants Antidepressive agents Antihypertensive agents Antipsychotic agents Arachidonic cascade modulators Aripiprazole Botulin toxin type a Bromocriptine Bupropion Calcium channel blockers Clomipramine Clozapine Cyproheptadine Desipramine Doxepin Fluperlapine Fluphenazine Imipramine Ketanserin Lisuride Loxapine Melatonin Metergoline Methiothepin Olanzapine Olcegepant Paliperidone Phenelzine Prochloreazine Prochlorperazine Protriptyline Quetiapine Risperidone Sertindole Spiperone	((((((((“brain-derived neurotrophic factor”[Title] OR 5-HT* [Title] OR "Alpha-T angoinst"[Title] OR Amitriptyline[Title] OR Amoxapine[Title] OR Anticonvulsants[Title] OR Antidepressive[Title] OR Antihypertensive[Title] OR Antipsychotic[Title] OR "Arachidonic cascade "[Title] OR Aripiprazole[Title]))))) OR (((Botulin[Title] OR Bromocriptine[Title] OR Bupropion[Title])) OR ("Calcium channel blocker"[Text Word] OR Clomipramine[Text Word] OR Clozapine[Text Word] OR Cyproheptadine[Text Word]))) OR ((((((Desipramine[Title] OR Doxepin[Title])) OR (Fluperlapine[Title] OR Fluphenazine[Title])) OR (Imipramine[Title] OR Ketanserin[Title] OR Lisuride[Title] OR Loxapine[Title])) OR (Melatonin[Title] OR Metergoline[Title] OR Methiothepin[Title])) OR (Olanzapine[Title] OR Olcegepant[Title]))) OR (((((Paliperidone[Title] OR Phenelzine[Title] OR Prochloreazine[Title] OR Prochlorperazine[Title] OR Protriptyline[Title])) OR (Quetiapine[Title] OR Risperidone[Title])) OR (Sertindole[Title] OR Spiperone[Title] OR Sulpiride[Title] OR Telcaegepant[Title] OR Tenilapine[Title] OR Textromethorphan[Title] OR Tonabersat[Title] OR Trifluoperazine[Title])) OR (Ziprasidone[Title] OR Zotepine[Title]))))) OR ((((((((((((((((((((("Drug Therapy"[Mesh] OR "drug therapy" [Subheading]) OR "Amoxapine"[Mesh]) OR ("Anticonvulsants"[Mesh] OR "Anticonvulsants" [Pharmacological Action])) OR ("Antidepressive Agents"[Mesh] OR "Antidepressive Agents" [Pharmacological Action])) OR ("Antihypertensive Agents"[Mesh] OR "Antihypertensive Agents" [Pharmacological Action])) OR ("Antipsychotic Agents"[Mesh] OR "Antipsychotic Agents" [Pharmacological Action])) OR ("Aripiprazole"[Mesh] OR "aripiprazole lauroxil" [Supplementary Concept])) OR "Bromocriptine"[Mesh]) OR "Botulinum Toxins"[Mesh]) OR "Bupropion"[Mesh]) OR ("Calcium Channel Blockers"[Mesh] OR "Calcium

Sulpiride Telcaegepant Tenilapine Textromethorphan Tonabersat Trifluoperazine Ziprasidone Zotepine	Channel Blockers" [Pharmacological Action])) OR "Clomipramine"[Mesh]) OR "Clozapine"[Mesh]) OR "Cyproheptadine"[Mesh]) OR "Doxepin"[Mesh]) OR "fluperlapine" [Supplementary Concept]) OR "Fluphenazine"[Mesh])) OR ((((((((((((((("Melatonin"[Mesh]) OR "Metergoline"[Mesh]) OR "Methiothepin"[Mesh]) OR "olanzapine" [Supplementary Concept]) OR "olcegepant" [Supplementary Concept]) OR "Paliperidone Palmitate"[Mesh]) OR "Phenelzine"[Mesh]) OR "Prochlorperazine"[Mesh]) OR "Protriptyline"[Mesh]) OR "Quetiapine Fumarate"[Mesh]) OR "Risperidone"[Mesh]) OR "Spiperone"[Mesh]) OR "Sulpiride"[Mesh]) OR "tonabersat" [Supplementary Concept]) OR "Trifluoperazine"[Mesh]) OR "ziprasidone" [Supplementary Concept]) OR "zotepine" [Supplementary Concept])))) OR "Amitriptyline"[Mesh])
NOT	
Not Editorials, etc.	((((((("Letter"[Publication Type]) OR "News"[Publication Type]) OR "Patient Education Handout"[Publication Type]) OR "Comment"[Publication Type]) OR "Editorial"[Publication Type])) OR "Newspaper Article"[Publication Type]
Limit to last 5 years ; human ; English	Filters activated: published in the last 5 years, Humans, English
N=418	
Systematic Review N=52	PubMed subsection “Systematic [sb]”
Randomized Controlled Trials N=320	Cochrane Sensitive Search Strategy for RCT’s “(((((((((groups[tiab])) OR (trial[tiab])) OR (randomly[tiab])) OR (drug therapy[sh])) OR (placebo[tiab])) OR (randomized[tiab])) OR (controlled clinical trial[pt])) OR (randomized controlled trial[pt])”
Other N=46	((((("JAMA"[Journal]) OR "The New England journal of medicine"[Journal]) OR "Lancet (London, England)"[Journal]) OR "BMJ (Clinical research ed.)"[Journal]) OR "Annals of internal medicine"[Journal]

Device Search

Topic: Devices for the prevention of Migraine Disorders Date: November 9th, 2016	Database Searched: MEDLINE (PubMed)
Concept	Search String
Devices	((((("Nerve stimulation"[Title/Abstract] OR device[Title/Abstract] OR "ovale closure"[Title/Abstract]))))
AND	
Migraine	"Migraine Disorders"[Mesh]
AND	
Prevention	((((Prophylaxis[Title/Abstract] OR prevent[Title/Abstract] OR prophylactic[Title/Abstract])))) OR ("prevention and control" [Subheading]))))

Limit to last 5	Filters activated: published in the last 5 years,
N=18	

Clinicaltrials.gov

Drug Search

Open Studies: Recruiting
32 studies found for: Prevention OR Prophylactic OR prophylaxis OR preventative OR Prevent OR Preventative | Recruiting | migraine | Studies received from 10/04/2011 to 10/04/2016
https://clinicaltrials.gov/ct2/results?term=Prevention+OR+Prophylactic+OR+prophylaxis+OR+preventative+OR+Prevent+OR+Preventative&recr=Recruiting&type=&rslt=&age_v=&gndr=&cond=migraine&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=10%2F04%2F2011&rcv_e=10%2F04%2F2016&lup_s=&lup_e=
Closed Studies
Active, not recruiting
13 studies found for: Prevention OR Prophylactic OR prophylaxis OR preventative OR Prevent OR Preventative | Active, not recruiting | migraine | Studies received from 10/04/2011 to 10/04/2016
https://clinicaltrials.gov/ct2/results?term=Prevention+OR+Prophylactic+OR+prophylaxis+OR+preventative+OR+Prevent+OR+Preventative&recr=Active%2C+not+recruiting&type=&rslt=&age_v=&gndr=&cond=migraine&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=10%2F04%2F2011&rcv_e=10%2F04%2F2016&lup_s=&lup_e=
Completed
31 studies found for: Prevention OR Prophylactic OR prophylaxis OR preventative OR Prevent OR Preventative | Completed | migraine | Studies received from 10/04/2011 to 10/04/2016
https://clinicaltrials.gov/ct2/results?term=Prevention+OR+Prophylactic+OR+prophylaxis+OR+preventative+OR+Prevent+OR+Preventative&recr=Completed&type=&rslt=&age_v=&gndr=&cond=migraine&intr=&titles=&outc=&spons=&lead=&id=&state1=&cntry1=&state2=&cntry2=&state3=&cntry3=&locn=&rcv_s=10%2F04%2F2011&rcv_e=10%2F04%2F2016&lup_s=&lup_e=

Device Search

17 studies found for: Prevent OR prophylaxis OR prophylactic | Migraine | Device | Studies received from 11/09/2011 to 11/09/2016
https://clinicaltrials.gov/ct2/results?term=Prevent+OR+prophylaxis+OR+prophylactic&cond=Migraine&intr=Device&rcv_s=11%2F09%2F2011&rcv_e=11%2F09%2F2016&show_down=Y