# Topic Brief: Combination Therapy for Migraines

**Date:** 5/9/2023
**Nomination Number:** 1034

**Purpose:** This document summarizes the information addressing a nomination submitted on November 17, 2022 (link to nomination) through the Effective Health Care Website. This information was used to inform the Evidence-based Practice Center (EPC) Program decisions about whether to produce an evidence report on the topic, and if so, what type of evidence report would be most suitable.

**Issue:** Migraine headaches detract from quality of life and increase the likelihood of comorbidities such as anxiety and depression. Many payers impose formulary restrictions on concomitant pharmaceutical treatments. The nominators are interested in the cost/benefit analysis of combination pharmaceutical treatments, including the use of new pharmaceutical treatments.

**Findings:** The EPC Program will not develop a new systematic review because we found systematic reviews addressing the concerns of this nomination.

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## Background

Migraine headaches are characterized by recurrent episodes of throbbing pain on one side of the head, and may include increased sensitivity to light, noise, and odors, nausea and vomiting.[1] In the United States, 1 in 6 adults and 1 in 5 women self-report migraine and severe headache over a 3-month period. Americans who experience higher rates of migraine include Indigenous Americans, adults between the ages of 18 and 44 years, and adults who are unemployed, low-income, or elderly and disabled. Headache is the fourth or fifth most common reason for emergency department visits,[2] and costs an estimated at $56 billion annually.[3]

Pharmaceutical treatments are either acute (taken to reduce occurring symptoms) or preventive (taken to prevent the occurrence of symptoms). Acute pharmaceutical interventions include drugs to reduce pain (e.g., triptans, ergot, nonsteroidal anti-inflammatory drugs) and relieve nausea. Preventive pharmaceutical interventions (e.g., antihypertensives, anticonvulsants, 5HT 1F receptor agonists) are taken daily or monthly to reduce occurrence or severity of headaches.[1] Many preventive pharmaceutical interventions for migraine exist. The nominators are interested in a review of preventive combination pharmaceuticals for headache that assesses the benefits and harms, patients' value and preferences, and cost-effectiveness.

## Scope

KQ 1: What are the benefits and harms of pharmacologic preventive treatment in adults with episodic migraine? With the following sub-question:

1.a Do treatment benefits and harms vary by demographic characteristics (age, sex, race/ethnicity)?

KQ 2: What is the cost-effectiveness of various pharmacologic preventive treatments in adults with episodic migraine?

**Table 1.** Questions and PICOs (population, intervention, comparator, outcome)

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|---|---|
| **Questions** | 1. Benefits and harms of pharmacologic preventive treatment of migraines.<br>2. Cost-effectiveness of pharmacologic preventive treatments. |
| **Population** | Adult (18 years or older) outpatients of all races and ethnicities with episodic migraine headache that prompt preventive pharmacologic therapy. Episodic migraines are defined as headache occurring on fewer than 15 days a month. |
| **Interventions** | Antidepressants<br>*Tricyclic Antidepressant<br>- Amitriptyline<br>- Doxepin<br>* Serotonin and Norepinephrine Reuptake Inhibitor<br>- Venlafaxine<br>- Fluoxetine<br>• Anticonvulsants / anti-epileptics<br>- Valproate products: divalproex sodium, sodium valproate/valproic acid<br>- Lamotrigine<br>- Topiramate<br>• Beta-Adrenergic Blockers<br>- Metoprolol<br>- Propranolol<br>• Calcitonin gene-related peptide (CGRP) receptor antagonists<br>- Atogepant<br>- Rimegepant<br>• CGRP antagonists- monoclonal antibody<br>- Eptinezumab<br>- Erenumab<br>- Fremanezumab<br>- Galcanezumab<br>• ACE inhibitors<br>- Lisinopril<br>- Captopril<br>- Enalapril<br>• ARBs<br>- Telmisartan<br>- Candesartan<br>• Calcium channel blockers<br>- Verapamil<br>• Other agents<br>- Pizotifen<br>Any combination therapy |
| **Comparators** | • Placebo or other inactive control<br>• One another intervention<br>• Combination with one another intervention |

| | |
|---|---|
| **Outcomes** | KQ 1:<br>Migraine-Focused Outcomes:<br>• Migraine frequency<br>• Migraine duration<br>• Acute medication intake days<br>• Emergency room visits<br>Patient reported outcomes:<br>• Migraine-related disability<br>• Quality of life<br>• Physical functioning<br>• Adverse events<br>• Discontinuation due to adverse events<br><br>KQ 2:<br>• Incremental costs<br>• Incremental benefits<br>• Incremental Cost-utility ratio (incremental cost per healthy years) |

## Assessment Methods

See Appendix A.

## Summary of Literature Findings

A systematic review of pharmaceutical interventions for the prevention of episodic migraine headaches that addresses the nomination is currently underway.[4]

See Appendix B for detailed assessments of all EPC selection criteria.

## Summary of Selection Criteria Assessment

Migraine headaches detract from quality of life and increase the likelihood of comorbidities such as anxiety and depression. Many payers impose formulary restrictions on concomitant pharmaceutical treatments. The nominators are interested in the cost/benefit analysis of combination pharmaceutical treatments, including the use of new pharmaceutical treatments. A systematic addressing the nomination is currently underway.

## References


1. Migraine. National Institute of Neurological Disorders and Stroke. doi: https://www.ninds.nih.gov/health-information/disorders/migraine.
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4. Damen JY, Bada; Vernooij, Robin, et. al. Pharmacological interventions for the prevention of episodic migraine headaches. PROSPERO. 2023. doi: https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=414305.


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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.

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# Appendix A: Methods

We assessed nomination for priority for a systematic review or other AHRQ Effective Health Care report with a hierarchical process using established selection criteria. Assessment of each criteria determined the need to evaluate the next one. See Appendix B for detailed description of the criteria.

## Appropriateness and Importance

We assessed the nomination for appropriateness and importance.

## Desirability of New Review/Absence of Duplication

Since the program was aware of the American College of Physician's plans to develop a systematic review on this topic, we did not conduct any searches for other ongoing or completed reviews.

# Appendix B. Selection Criteria Assessment

| Selection Criteria | Assessment |
|---|---|
| 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. |
| 1b. Is the nomination a request for an evidence report? | Yes. |
| 1c. Is the focus on effectiveness or comparative effectiveness? | Yes. |
| 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. |
| 2. Importance | |
| 2a. Represents a significant disease burden; large proportion of the population | Migraine headaches are characterized by recurrent episodes of throbbing pain on one side of the head, and may include increased sensitivity to light, noise, and odors, nausea and vomiting. [1] In the US, 1 in 6 adults and 1 in 5 women self-report migraine and severe headache over a 3-month period. Americans who experience higher rates of migraine include Indigenous Americans, people between the ages of 18 and 44 years, and people who are unemployed, low-income, or elderly and disabled. |
| 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 | Migraine headaches are characterized by recurrent episodes of throbbing pain on one side of the head, and may include increased sensitivity to light, noise, and odors, nausea and vomiting. [1] In the US, 1 in 6 adults and 1 in 5 women self-report migraine and severe headache over a 3-month period. Americans who experience higher rates of migraine include Indigenous Americans, people between the ages of 18 and 44 years, and people who are unemployed, low-income, or elderly and disabled. Headache is the fourth or fifth most common reason for emergency department visits,[2] and costs an estimated $56 billion annually.[3] |
| 2c. Incorporates issues around both clinical benefits and potential clinical harms | Yes. |
| 2d. 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 | Headache is the fourth or fifth most common reason for emergency department visits,[2] and costs an estimated $56 billion annually.[3] |
| 3. Desirability of a New Evidence Review/Absence of Duplication | |
| 3. A recent high-quality systematic review or other evidence review is not available on this topic | Yes. The American College of Physicians is currently conducting a systematic review covering the nomination.[4] |