

Acute Treatments for Episodic Migraine

Evidence Summary



Main Points

- Compared with placebo, treatments such as triptans, NSAIDs (nonsteroidal anti-inflammatory drugs), dihydroergotamine, antiemetics, and acetaminophen, reduce pain but increase the risk of mild and transient adverse events.
- Only a small number of studies have evaluated opioids. Some opioids may reduce pain of episodic migraine. Some opioids may be less effective than other drugs.
- No studies evaluate instruments for predicting risk of opioid misuse, opioid use disorder or overdose, or evaluate risk mitigation strategies to be used when prescribing opioids for episodic migraine.
- Newer therapies such as calcitonin gene-related peptide receptor antagonists and lasmiditan (5-HT_{1F} receptor agonist) probably improve pain relief at 2 hours and increase the likelihood of being pain-free at 2 hours, 1 day, and at 1 week, and restore function. Serious adverse events are more common in patients who received lasmiditan than placebo.
- Although only studied in one or a few small trials, several other therapies available in the United States may improve migraine pain compared with placebo, including dexamethasone, dipyrrone, lidocaine, magnesium sulfate octetate, and secobarbital. Evidence is insufficient to draw conclusions about serious adverse events.
- Although only studied in one or a few small trials, several nonpharmacological treatments for migraine may improve various measures of pain migraine compared with placebo, including noninvasive neuromodulation devices such as remote electrical neuromodulation, magnetic stimulation, and external trigeminal nerve stimulation, as well as other therapies such as acupuncture, chamomile oil, and eye movement desensitization reprocessing. Evidence is insufficient to draw conclusions about serious adverse events.





Background and Purpose

In patients with migraine, several acute treatment options are available, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy.¹ Current guidelines recommend the use of triptans and NSAIDs as first line acute treatments, as well as acetaminophen for non-incapacitating attacks.² However, the evidence supporting the effectiveness of opioids, other nonopioid pharmacologic therapy, and nonpharmacologic therapies remains unclear. Evidence about harms is also unclear. Opioid and butalbital-containing medications have a two-fold higher risk of medication overuse headache compared with simple analgesics and triptans.³ Additionally, the use of opioids for the acute treatment of migraine has been identified as a risk factor for disease chronification.^{4,5} Thus, the American Headache Society recommends that opioids and butalbital-containing drugs should not be used as first-line treatment for migraine and other recurrent headache disorders, and guidelines recommend that triptans and simple analgesics should be tried first.⁶ If triptans and NSAIDs are ineffective, contraindicated or not tolerated, patients and clinicians struggle when deciding how to use these other therapies. They need information about the comparative effectiveness and harms of alternative therapies to the first line treatments of triptans and NSAIDs.

This systematic review assesses the comparative effectiveness and harms for acute migraine treatments, including opioid therapy, nonopioid pharmacologic therapy, and nonpharmacologic therapy.



Methods

We followed the established methodologies of systematic reviews as outlined in the Agency for Healthcare Research and Quality Methods Guide for Effectiveness and Comparative Effectiveness Reviews.⁷ The reporting complies with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements.⁸ The study protocol was published on AHRQ website (<https://effectivehealthcare.ahrq.gov/products/migraine-treatments/protocol>) and was registered to the International Prospective Register of Systematic Reviews (PROSPERO #: CRD42020163262).



Results

Evidence on triptans and nonsteroidal anti-inflammatory drugs (NSAIDs) was summarized from 16 existing systematic reviews. For other interventions, we identified 15,247 citations from which we included 141 original studies with a total of 37,653 patients (Appendix Figure A.1.).

Key Question (KQ) 1: Opioid Therapy

- Fifteen studies (13 randomized controlled trials [RCTs] and 2 comparative observational studies) with 2,208 patients were included for KQ1.
- No studies evaluated instruments for predicting risk of opioid misuse, opioid use disorder or overdose; or evaluated risk mitigation strategies in episodic migraine.

Effectiveness and harms:

- Tramadol in combination with acetaminophen may reduce pain at 2 hours and 1 day, compared with placebo (low strength of evidence [SOE]). However, the evidence for tramadol alone was insufficient. Tramadol plus acetaminophen was associated with significantly increased number of adverse events (AEs).
- Butorphanol may reduce pain at 2 hours, 1 day, and 1 week, compared with placebo (low SOE). It was associated with increased number of gastrointestinal AEs, neurological AEs, and total number of AEs.
- Evidence was insufficient to draw conclusions about serious adverse events.

Comparative effectiveness and harms:

- Meperidine plus hydroxyzine may be worse than dihydroergotamine plus metoclopramide in terms of pain relief at 2 hours and function (low SOE).
- Morphine may be worse than intravenous dexamethasone in terms of pain relief at 2 hours and 1 day (low SOE).
- Hydromorphone may be worse than metoclopramide (low SOE) and worse than diphenhydramine plus prochlorperazine in terms of pain relief at 2 hours (low SOE). Evidence was insufficient to draw conclusions about serious adverse events.

KQ2: Nonopioid Pharmacologic Therapy

- Evidence on triptans and NSAIDs was summarized from 16 existing systematic reviews. Data on triptans were derived from 186 RCTs summarized in 9 systematic reviews (101,276 patients), data on NSAIDs were derived from 5 systematic reviews (46 RCTs, 13,214 patients) and two systematic reviews evaluated the combination of triptans and NSAIDs. One hundred ten articles of 108 studies (105 RCTs and 3 comparative observational studies) and 33,687 patients were included for other interventions.

Effectiveness and harms of established treatments:

- Compared with placebo, triptans resolve pain at 2 hours and 1 day (high SOE), and increase the risk of mild and transient adverse events (high SOE).
- Compared with placebo, NSAIDs probably resolve pain at 2 hours and 1 day (moderate SOE), and increase the risk of mild and transient adverse events (moderate SOE).
- Compared with placebo, dihydroergotamine reduces pain (high SOE) and probably increases the likelihood of being pain free at 2 hours, 1 day and 1 week (moderate

- SOE). Dihydroergotamine probably improves function (moderate SOE) and improves sustained pain relief (high SOE) at 2 hours and 1 day.
- Compared with placebo, ergotamine plus caffeine probably improves pain relief at 2 hours (moderate SOE).
 - Antiemetics, including prochlorperazine, chlorpromazine, metoclopramide, droperidol and haloperidol, may resolve pain at 2 hours and 1 day (low SOE) compared with placebo.
 - Evidence was insufficient across all pharmacological treatments to draw conclusions about serious adverse events.

Effectiveness and harms of newer treatments:

- Compared with placebo, calcitonin gene-related peptide receptor (CGRP) antagonists (known as gepants), including rimegepant, and ubrogepant, demonstrated improved pain relief at 2 hours (moderate to high SOE) and increased the likelihood of being pain free at 2 hours (moderate to high SOE) and sustained pain free at 1 day and at 1 week (moderate to high SOE). Evidence was insufficient to draw conclusions about serious adverse events.
- Compared with placebo, the 5-HT_{1F} receptor agonist lasmiditan restored function at 2 hours (high SOE), and also resolved pain at 2 hours (high SOE), 1 day (high SOE) and 1 week (moderate SOE). Serious adverse events were more common in patients who received lasmiditan than placebo (high SOE).

Other comparisons:

- Although only studied in one or a few small trials, several other therapies may improve migraine pain compared with placebo, including dexamethasone, dipyrone, lidocaine, magnesium sulfate, octreotide, and secobarbital (low SOE). Evidence was insufficient to draw conclusions about serious adverse events.

KQ3: Nonpharmacologic Therapy

- Seventeen RCTs and one comparative observational study with 1,758 patients were included for KQ3.
- Although only studied in one or a few small trials, several nonpharmacological acute treatments of migraine may improve various measures of pain compared with placebo, including acupuncture (low SOE), chamomile oil (low SOE), external trigeminal nerve stimulation (low SOE), eye movement desensitization reprocessing (low SOE), and remote electrical neuromodulation (moderate SOE).
- Evidence was insufficient to draw conclusions about serious adverse events.



Limitations

For many interventions, very few or a single trial were available and most were small, which limits inferences from the quantitative analysis. The studies were conducted in different settings, from the emergency room to outpatient to inpatient environments. This review does not capture harms that may arise with frequent or long-term intermittent use of the treatments. The inability to capture such harms is due to study design as the

majority of trials evaluate the efficacy and harms of the treatments during one or a few attacks. In terms of applicability, several of the established drugs, such as the ergot alkaloids, may not be reliably stocked by pharmacies and some of newer drugs may not be accessible or afforded by all patients. Finally, patients are often advised to use combinations of therapies to treat migraine attacks. This combination can include an antiemetic as well as migraine specific therapy such as a triptan and a nonspecific analgesic such as an NSAID. The trials we analyzed did not sufficiently evaluate these potential combination therapies and their interactions.



Implications and Conclusions

High and moderate strength of evidence support the effectiveness of triptans and NSAIDs, respectively. These established treatments, along with dihydroergotamine, antiemetics and acetaminophen, are considered established acute treatments for migraine. In general, adverse events of these drugs are mild and transient.

A common challenge in practice is when certain patients do not have pain relief with, or do not tolerate, these established treatments. Newer therapies for acute treatment of migraine such as the calcitonin gene-related peptide antagonists (known as gepants) and the 5-HT_{1F} receptor agonist, lasmiditan, were more effective than placebo in improving pain relief at 2 hours and 1 day and at 1 week. However, adverse events of newer medications require further study. For example, lasmiditan increased the risk of serious adverse events compared with placebo. Additionally, several nonpharmacologic acute treatments for migraine are available; however, they have been in studied in one or a few small trials.

This systematic review has shown that very few studies evaluated the use of opioids for acute migraine. The strength of evidence supporting the use of the various opioids for acute treatment of migraine was low or insufficient. No included studies evaluated instruments to help in predicting risk of opioid misuse, developing opioid use disorders or overdose in patients with migraine. No included studies evaluated risk mitigation strategies to be used when prescribing opioids for episodic migraine. The lack of risk assessment tools and mitigation strategies has major implications for practical implementation of treatment algorithms that include opioids. When this is viewed in the context of how widely opioids are prescribed for migraine management, it is particularly concerning.⁹⁻¹⁵

The findings of this systematic review can inform shared decision making and choice of therapy. With this information, the place for newer therapies (ex. gepants, ditans and neuromodulatory devices) can be identified among established therapies. Furthermore, the discrepancy between evidence and historical prescribing practices, such as with opioids, has been highlighted.



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Full Report

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