Comparative Effectiveness Review
Number 84

Effective Health Care Program

# Acute Migraine Treatment in Emergency Settings

## *Executive Summary*

### Introduction

Migraine is a chronic neurovascular disorder characterized by dysfunction of the central and peripheral nervous systems and intracranial vasculature.[1] Acute exacerbations of episodic and chronic migraine cause severe and disabling pain that often results in visits to an emergency department (ED), as well as decreased productivity and missed time from work, school, and other activities.[2] Migraine has a negative impact on overall quality of life[3] and is associated with psychiatric and medical comorbidities.[4,5] In the United States, migraine and related medical issues result in costs of more than $13 billion per year due to lost productivity.[6]

Migraine causes acute headaches, which typically last 4 hours to 3 days if untreated. Most individuals with migraine are able to treat their attacks at home; however, this treatment is not always successful. Furthermore, when the initial oral treatment for acute severe headaches fails, subsequent attempts are likely to fail as well. Of Americans with migraine, 7 percent were reported to use an ED or urgent care center for treatment of severe headache within the previous 12 months.[7] In the United States, headaches accounted for 2.1 million ED visits annually, 2.2 percent of all ED visits.[8] Migraine sufferers who use the ED often report multiple ED visits annually.[7]

### Effective Health Care Program

The Effective Health Care Program was initiated in 2005 to provide valid evidence about the comparative effectiveness of different medical interventions. The object is to help consumers, health care providers, and others in making informed choices among treatment alternatives. Through its Comparative Effectiveness Reviews, the program supports systematic appraisals of existing scientific evidence regarding treatments for high-priority health conditions. It also promotes and generates new scientific evidence by identifying gaps in existing scientific evidence and supporting new research. The program puts special emphasis on translating findings into a variety of useful formats for different stakeholders, including consumers.

The full report and this summary are available at **www.effectivehealthcare.ahrq.gov/reports/final.cfm**.

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Effective Health Care

While headache is a common cause of presentation to the ED, there is substantial practice variability among emergency clinicians.[9-12] Twenty disparate parenteral agents are used to treat acute migraine in EDs in the United States.[9] Among the agents used are 5-hydroxytryptamine (HT) receptor agonists (e.g., triptans), dopamine receptor antagonists (e.g., phenothiazines, metoclopramide), ergot derivatives (e.g., dihydroergotamine [DHE]), intravenous (IV) nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids. The most common first-line agents for migraine treatment include opioids; however, in more recent research studies, metoclopramide and prochlorperazine, a phenothiazine, appear to be increasingly used.[13-15] While alternative phenothiazines exist, prochlorperazine is usually preferred due to its efficacy and safety.[16,17] IV DHE and ketorolac are also used to treat acute migraine. Opioids are often used to treat acute migraine, despite their recognized ability to cause dependence and their association with a higher risk of headache relapse.[18] Some physicians use agents sequentially (e.g., metoclopramide followed by ketorolac if patients are not fully recovered following a 30-60–minute assessment period); however, the use of a combination treatment is also popular (e.g., metoclopramide and ketorolac administered simultaneously). Table A summarizes pharmacological interventions that have been approved by the U.S. Food and Drug Administration and that are used, often off label, for acute migraine.

## Scope and Key Questions

The first objective of this Comparative Effectiveness Review (CER) is to assess the effectiveness of various parenteral medications for adult patients with moderate to severe acute migraine who present to an ED for treatment. The second objective is to assess important immediate and short-term side effects of the different interventions. This CER will specifically investigate akathisia associated with metoclopramide and phenothiazines. A third focus is to examine the benefit and risk of using corticosteroids for preventing recurrence of acute migraine that results in a return visit to a physician or ED.

**Table A. Summary of pharmacological interventions for acute migraine**

| Intervention | Generic Name | Trade Name(s) | Mode of Administration |
|---|---|---|---|
| Agents for Procedural Sedation | Ketamine | Ketalar | IV, IM |
| | Ketofol | NA | IV |
| | Propofol | Diprivan, Lusedra | IV |
| | Anticonvulsants | | |
| | Magnesium sulfate | Magnesium sulfate | IV, IM |
| | Valproic acid | Depacon | IV |
| Antiemetics | Metoclopramide | Maxeran | IM |
| | | Reglan | IV, IM |
| | Trimethobenzamide | Tigan, Tebamide | IM |
| Corticosteroids | Betamethasone | Celestone, Soluspan | IM |
| | Budesonide | Entocort EC | Oral |
| | Cortisone | Cortone | Oral, IM |
| | Dexamethasone | Decadron | IM, IV |
| | Hydrocortisone | Solu-Cortef | Oral |
| | Methylprednisolone | Depo-Medrol | IM |
| | | Solu-Medrol | IV, IM |
| | Prednisolone | Prelone | Oral |
| | Prednisone | Deltasone | Oral |
| Ergots | Dihydroergotamine | DHE 45 | IV, IM, SC |
| | NSAIDs | | |
| | Ketorolac | Toradol | IV, IM |

| Table A. Summary of pharmacological interventions for acute migraine (continued) | | | |
|---|---|---|---|
| **Intervention** | **Generic Name** | **Trade Name(s)** | **Mode of Administration** |
| Opioids | Butorphanol | Butorphanol tartrate | IV, IM |
| | Buprenorphine | Buprenex | IM, IV |
| | Fentanyl | Sublimaze | IM, IV |
| | Hydromorphone | Dilaudid | SC, IM, IV |
| | Meperidine (pethidine) | Demerol | IV, IM |
| | Morphine | Apokyn | SC |
| | | Astramorph PF, DepoDur, Duramorph PF, Infumorph | IV |
| | Nalbuphine | Nubain | SC, IM, IV |
| | Tramadol | Conzip, Ryzolt, Ultracet, Ultram, Ralivia, Zytram XL | Oral, IM, IV |
| Neuroleptics | Chlorpromazine | Largactil | IV, IM |
| | Droperidol | Inapsine | IV, IM |
| | Haloperidol | Haldol | IV, IM |
| | Prochlorperazine | Stemetil, Compazine (other modes available) | IV, IM |
| Triptan Agents | Sumatriptan | Alsuma, Imitrex (other modes available), Sumavel DosePro | SC |
| Other Agents | Hydroxyzine | Atarax, Vistaril | Oral, IM |
| | Lidocaine | Xylocaine | IV, SC |
| | Promethazine | Phenergan | IV, IM |

DHE = dihydroergotamine; IM = intramuscular; IV = intravenous; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory drugs; SC = subcutaneous

The Key Questions (KQs) are as follows:

1. What is the comparative effectiveness of parenteral pharmacological interventions versus standard care, placebo, or an active treatment in the treatment of acute migraine headaches in adults visiting the ED?
2. What is the comparative effectiveness of adding parenteral or oral corticosteroids versus adding placebo to acute parenteral pharmacological interventions to prevent recurrence of acute migraine headaches in adults after being treated in the ED?
3. What are the associated short-term adverse effects of these parenteral pharmacological interventions, and do they differ across interventions?
4. Does the development of adverse events (especially akathisia) differ following the administration of anticholinergic agents and phenothiazines when compared with anticholinergic agents and metoclopramide?
5. Do the effectiveness and safety of the parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and nonresponders while in the ED?
6. Do the effectiveness and safety of adding parenteral or oral corticosteroids to acute parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and nonresponders?

Figure A provides an analytic framework to illustrate the population (P), interventions (I), control/comparison (C), and outcomes (O) that guided the literature search and synthesis. This figure depicts the KQs within the context of the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting). In general, the figure illustrates a comparison of parenteral pharmacological interventions and parenteral or oral corticosteroid interventions versus standard care, placebo, or an active comparator in terms of intermediate outcomes such as time in ED, recurrence

of severe symptoms, or return ED visits within 24 to 48 hours, and final outcomes such as pain relief, satisfaction with experience, quality of life, and return to activities. Adverse effects may occur at any point after the treatment is received and were assessed up to 3 months postintervention.

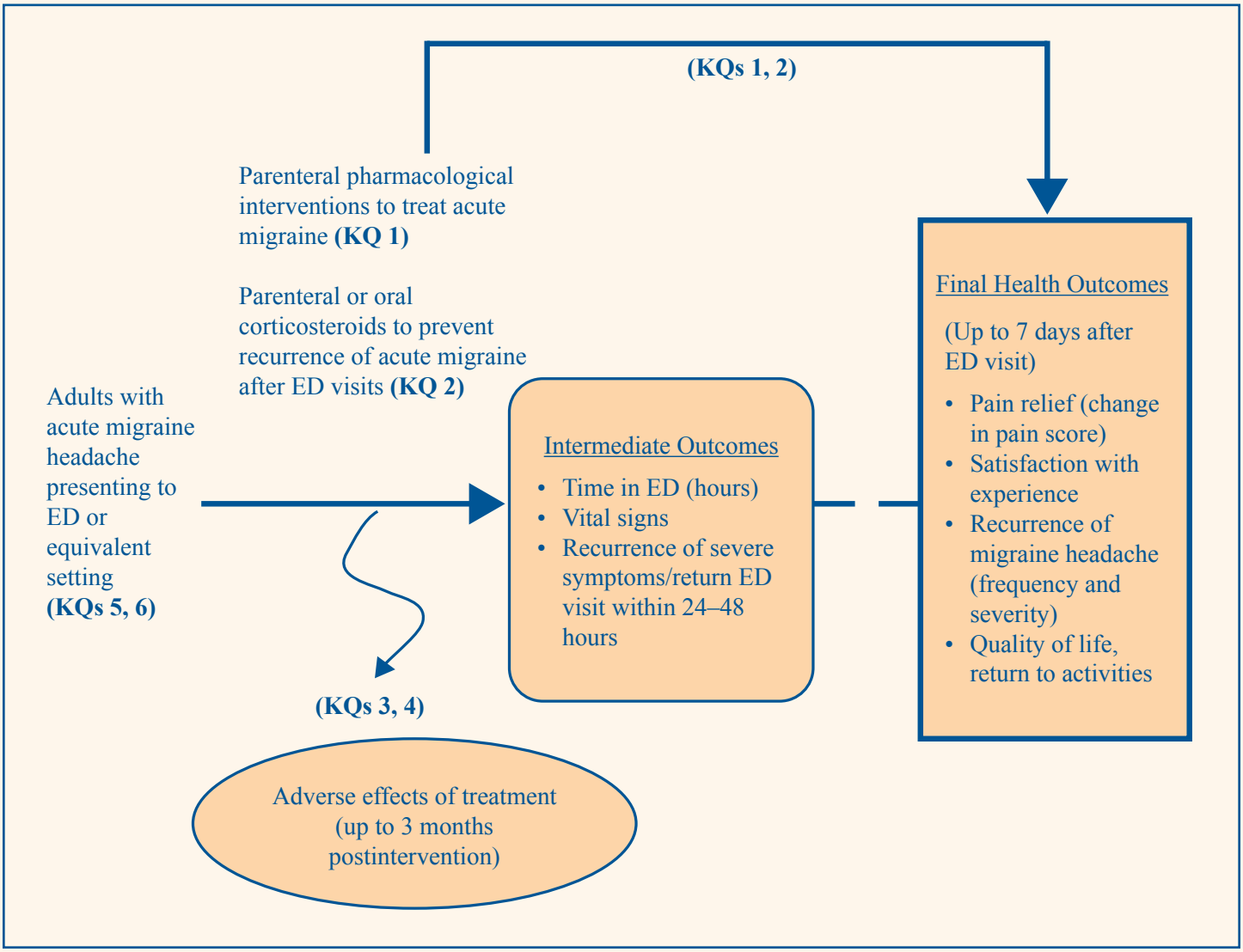
## Methods

The methods section reflects the protocol that was developed a priori as part of the topic development and refinement stages of this CER.

### Topic Refinement and Review Protocol

The University of Alberta Evidence-based Practice Center (EPC) was commissioned to conduct a preliminary literature review to gauge the availability of evidence and to draft key research questions for a CER. Investigators from the EPC developed the KQs in consultation with the Agency for Healthcare Research and Quality (AHRQ) EPC Program, the Scientific Resource Center, and a panel of Key Informants. AHRQ posted the KQs on their Web site for public comment for a period of 1 month. The EPC revised the KQs based on the public feedback, and AHRQ

**Figure A. Analytic Framework**




KQ = Key Question; ED = emergency department

approved the final KQs. A Technical Expert Panel was assembled to provide content and methodological expertise throughout the development of the CER.

### Literature Search Strategy

A research librarian systematically searched the following electronic databases: MEDLINE®, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, International Pharmaceutical Abstracts, PASCAL, Biosis Previews, Science Citation Index Expanded, and Conference Proceedings Citation Index-Science. Databases were searched from inception to January 5, 2012. The search strategy did not employ any study design search filters, nor were language restrictions applied.

Reference lists of included studies and relevant systematic reviews were screened to identify additional studies. The following online trial registries were searched to identify unpublished and ongoing trials: ClinicialTrials.gov, metaRegister of Controlled Trials, World Health Organization International Clinical Trials Registry Platform, and CenterWatch. U.S. Food and Drug Administration documents related to the drugs of interest were reviewed for additional data. The Scientific Resource Center contacted drug manufacturers to request published and unpublished study data. Hand searches of conference proceedings were completed for the following scientific meetings: American College of Emergency Physicians, Society for Academic Emergency Medicine, American Headache Society, International Headache Society, American Neurological Association, Canadian Neurological Association, European College of Neuropsychopharmacology, International Neuropsychological Society, American Pain Society, Canadian Pain Society, and International Association for the Study of Pain. The Web sites of key organizations in emergency medicine, pain, headache, neuropharmacology, and neurology were searched for relevant research.

### Inclusion and Exclusion Criteria

The eligibility criteria were developed in consultation with the Technical Expert Panel. Randomized controlled trials (RCTs), nonrandomized controlled trials (NRCTs), and cohort studies that examined adults ≥18 years of age with moderate to severe acute migraine headache presenting to an ED or equivalent setting were included. Equivalent settings included headache or pain clinics, neurology departments, and physician offices in which parenteral administration of the interventions took place. For first-line ED treatment, eligible studies compared parenteral (IV, intramuscular, or subcutaneous) interventions with standard care, placebo, or an active comparator (any route of administration). For prevention of relapse, eligible studies compared corticosteroids (parenteral or oral) plus a standard parenteral therapy with standard parenteral therapy alone or with a placebo.

### Study Selection

The eligibility of studies was assessed in two phases. First, two reviewers independently screened titles and abstracts (where available) to determine if an article met broad inclusion criteria. Each article was rated as "include," "exclude," or "unclear." Second, a single reviewer screened U.S. Food and Drug Administration reports, conference proceedings, and gray literature for potential relevance. The full text of articles identified as "include" or "unclear" by at least one reviewer was retrieved. Finally, two reviewers independently assessed the full text of each study using a detailed form. Disagreements were resolved by consensus or third-party adjudication.

### Data Extraction

One reviewer extracted data, and a second reviewer verified the data for accuracy and completeness. Any discrepancies were resolved by consensus or third-party adjudication.

We recognize that many drugs have various effects. (For example, a neuroleptic can be used for the antiemetic treatment of nausea and vomiting.) In consultation with the Technical Expert Panel, the research team organized drugs by the classes outlined in Table A. For each drug class (e.g., neuroleptics), the trials with monotherapy compared with placebo are presented, followed by trials in which the monotherapy is compared with another active treatment (e.g., neuroleptics vs. metoclopramide). Combination therapies compared with an active comparator (e.g., metoclopramide plus DHE vs. ketorolac) are presented as a separate category. For the pain-related outcomes, drugs that have been added to the pain intervention in order to specifically deal with side effects are grouped with the main drug class. For example, prochlorperazine plus antihistamine vs. metoclopramide was included in the category of neuroleptics vs. metoclopramide.

We extracted adverse-effect data as they were reported by the authors of each study. The adverse effects of interest were determined a priori in consultation with the Technical Expert Panel. Due to variable comparisons and

reporting, the frequency of adverse effects was examined for individual arms of the trials and not as comparisons of effectiveness. For each adverse effect, the number of patients in each treatment group (e.g., intervention, placebo) and the number of patients with an adverse effect were recorded.

### Quality (Risk-of-Bias) Assessment

We assessed the internal validity of trials using the Cochrane Collaboration risk-of-bias tool.[19] In addition, the funding source for each study was extracted. Two reviewers independently assessed the risk of bias of the studies and resolved discrepancies through consensus. A priori decision rules were developed regarding application of the tool.

### Data Analysis

Evidence tables for all studies and a qualitative description of results are presented in the full report. Meta-analyses using random-effects models were conducted when studies were sufficiently similar in terms of design, population, interventions, and outcomes. Statistical heterogeneity was quantified using the I-squared ($I^2$) statistic.

A traditional pairwise meta-analysis of adverse effects was not performed, since we did not identify multiple studies with the same comparisons (e.g., prochlorperazine vs. magnesium sulfate) that reported common adverse effects. Instead, we present a summary of drug-related adverse effects by treatment arm that provides an overall picture of which interventions had a high risk of specific adverse effects. For each adverse-effect category, risks (i.e., incidence rates) were pooled using a random-effects model to obtain a summary estimate and 95% confidence interval (CI).

For two outcomes, pain relief and akathisia, a mixed-treatment analysis was conducted using a Bayesian network model to compare all interventions simultaneously.[20-22] Results are reported with 95-percent credible intervals. We checked the analyses for consistency using cross-validation of all contrasts that had direct evidence.[23]

### Applicability

The applicability of the body of evidence was assessed following the PICOTS format used to assess study characteristics.[24] Specific factors that were considered included sex, age, race or ethnicity, baseline headache severity, clinical setting (e.g., non-ED), and geographic setting (e.g., countries other than in North America).

### Grading the Body of Evidence

Two independent reviewers graded the body of evidence using the EPC Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach[25] and resolved discrepancies by consensus. The key effectiveness outcomes for KQs 1, 2, 5, and 6 were pain and headache recurrence. For KQ 3, we did not grade outcomes because there were no comparative effectiveness analyses. For KQ 4, the key outcome was the development of akathisia. Four major domains were assessed: risk of bias (low, moderate, or high), consistency (consistent, inconsistent, or unknown), directness (direct or indirect), and precision (precise or imprecise). The overall strength of evidence was graded as high, moderate, low, or insufficient. Single trials, particularly those with small sample sizes, were graded as having insufficient strength of evidence despite being precise and having low risk of bias. We did not make estimates regarding precision when it was inappropriate to pool results from studies.

## Results

### Description of Included Studies

The searches identified 3,138 citations from electronic databases. Screening based on titles and abstracts, gray literature searches, and hand-searching identified 231 potentially relevant studies. Seventy-one unique studies (69 RCTS, 2 NRCTs) met the eligibility criteria.

Nine different classes of drugs were investigated: antiemetics (metoclopramide), neuroleptics, ergotamines, NSAIDs, opioids, corticosteroids, triptans, magnesium sulfate ($MgSO_4$), and antihistamines. In addition, several studies examined combinations of active agents compared with other active agents. For the mixed-treatment analysis, we identified a group of drugs that were not easily classified and were infrequently studied (i.e., hydroxyzine [Atarax], lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide). We refer to these drugs collectively as "orphan agents."

The studies were published between 1986 and 2011. The majority were conducted in North America (75 percent). Sample sizes varied, with an overall median of 64 patients per study (interquartile range: 40 to 100). For the majority of studies, pain relief or severity was the primary outcome.

In 43 studies (61 percent), migraine was classified using criteria established by the International Headache Society.

### Methodological Quality of Included Studies

Overall, 43 trials (60.6 percent) had an unclear risk of bias, 20 (28.2 percent) had low risk, and 8 (11.3 percent) had high risk of bias. Risk of bias was generally low for incomplete outcome data, selective reporting, and "other bias." This means that these methodological sources of bias were uncommon in this body of evidence.

Twelve studies were funded by industry, seven were funded by associations and foundations, one received government funding, and two had other sources of funding.

### Key Findings

#### Key Question 1: Effectiveness of Parenteral Interventions Versus Placebo or an Active Treatment

Table B summarizes the outcomes and strength of evidence for KQ 1. Data are not presented in the table for comparisons for which there is insufficient evidence. These results can be found in the full report.

The mixed-treatment analysis showed that the most effective treatments were combination therapy (i.e., DHE added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low strength of evidence [SOE]), with a pain reduction of approximately 40 mm on the visual analog scale (VAS) (Table B). Metoclopramide monotherapy, opioids, and NSAIDs were the next most effective treatments, with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective, with a pain reduction of approximately 12-16 mm.

Metoclopramide was compared with placebo in six trials and with other active treatments in nine trials (Table B). Metoclopramide was significantly more effective than placebo for pain relief (moderate SOE). In general, neuroleptics were more effective than metoclopramide for pain relief (low SOE). Results for pain relief were inconsistent when comparing metoclopramide monotherapy with other active treatments, including $MgSO_4$, ondansetron plus paracetemol, pethidine, and sumatriptan. The SOE for these comparisons is insufficient to draw conclusions because they were based on single trials. The mixed-treatment analysis, which used direct and indirect evidence from multiple RCTs, demonstrated that, as monotherapy, metoclopramide was similarly effective to opioids and NSAIDs for pain relief (low SOE). There was insufficient SOE for headache recurrence when comparing metoclopramide with $MgSO_4$ or prochlorperazine.

Neuroleptics were compared with placebo in 7 trials and with other active treatments in 17 trials (Table B). Neuroleptics were more effective than placebo for VAS-rated pain intensity (moderate SOE), headache relief at 1 hour (moderate SOE), pain-free status at 1 hour (moderate SOE), and headache recurrence (low SOE). More patients who received droperidol than patients who received prochlorperazine experienced headache relief (moderate SOE). For all other head-to-head comparisons, single trials compared different neuroleptics with anticonvulsants, corticosteroids, DHE, other neuroleptics, opioids, somatostatin analog, sumatriptan, and lidocaine (insufficient SOE). The mixed-treatment analysis demonstrated that monotherapy with neuroleptic agents was one of the more effective treatment options for VAS-rated pain relief (low SOE). Single trials compared neuroleptic agents with another active agent for headache recurrence (insufficient SOE).

NSAIDs were compared with placebo in two trials and with other active treatments in nine trials (Table B). NSAIDs were more effective than placebo for pain-free status between 1 and 2 hours (moderate SOE). There was insufficient SOE for headache recurrence when NSAIDs were compared with placebo. Results were mixed for NSAIDs compared with other active agents for pain relief. Single trials compared NSAIDs with meperidine, sumatriptan, paracetamol, DHE, and tramadol (insufficient SOE). The mixed-treatment analysis demonstrated that NSAIDs were similarly effective to opioids and metoclopramide for VAS-rated pain relief (low SOE). There was insufficient SOE for headache recurrence when NSAIDs were compared with active agents.

Opioids were compared with placebo in 3 trials and with other active treatments in 13 trials (Table B). Opioids were more effective than placebo for pain relief (moderate SOE). Results were mixed for opioids compared with other active agents for pain relief. Single trials compared opioids with other opioids (e.g., nalbuphine, meperidine), hydroxyzine, methotrimeprazine, metoclopramide, neuroleptic agents, NSAIDs, dexamethasone, and DHE (insufficient SOE). The mixed-treatment analysis demonstrated that opioids were similarly effective to NSAIDs and metoclopramide for VAS-rated pain relief (low SOE).There was insufficient SOE for headache recurrence when comparing opioids and other active agents.

**Table B. Summary of strength of evidence for the effectiveness of parenteral interventions for acute migraine versus placebo or an active treatment (Key Question 1)**

| Intervention | Outcome | Comparison (# of Studies) | SOE | Summary |
|---|---|---|---|---|
| Metoclopramide | Pain intensity–VAS | Metoclopramide vs. placebo (5 RCTs) | Moderate | Significant effect in favor of metoclopramide (MD = -21.88; 95% CI, -27.38 to -16.38; $I^2$ = 0%) |
| | Change in pain–VAS | Metoclopramide vs. neuroleptics (4 RCTs) | Low | Significant effect in favor of neuroleptics (MD = 16.45; 95% CI, 2.08 to 30.83; $I^2$ = 81%) |
| | Change in pain–VAS | Metoclopramide vs. prochlorperazine (2 RCTs) | Low | No significant difference between groups (MD = 19.27; 95% CI, -8.85 to 47.38; $I^2$ = 90%) |
| Neuroleptics | Pain intensity–VAS | Neuroleptics vs. placebo (4 RCTs) | Moderate | Significant effect in favor of neuroleptics (MD = -46.59; 95% CI, -54.87 to -38.32, $I^2$ = 46%) |
| | Headache relief (1 hr) | Neuroleptic vs. placebo (5 RCTs) | Moderate | Significant effect in favor of neuroleptics (RR = 2.69; 95% CI, 1.66 to 4.34; $I^2$ = 76%) |
| | Pain free (1 hr) | Neuroleptic vs. placebo (4 RCTs) | Moderate | Significant effect in favor of neuroleptics (RR = 3.38; 95% CI, 1.16 to 9.83; $I^2$ = 90%) |
| | Headache recurrence (24 hrs) | Neuroleptic vs. placebo (2 RCTs) | Low | No significant difference between groups (RR = 0.46; 95% CI, 0.19 to 1.10; $I^2$ = 78%) |
| | Change in pain–VAS | Metoclopramide vs. prochlorperazine (2 RCTs) | Low | No significant difference between groups (MD = 19.27; 95% CI, -8.85 to 47.38; $I^2$ = 90%) |
| | Change in pain–VAS | Prochlorperazine vs. droperidol (2 RCTs) | Low | No significant difference between groups (MD = 9.12; 95% CI, -8.62 to 26.86) |
| | Headache relief | Prochlorperazine vs. droperidol (2 RCTs) | Moderate | Significant effect in favor of droperidol (RR = 0.81; 95% CI, 0.68 to 0.98) |
| NSAIDs | Pain free at 1–2 hrs | NSAIDs vs. placebo (2 RCTs) | Moderate | Significant effect in favor of NSAIDs (RR = 2.74; 95% CI, 1.26 to 5.98; $I^2$ = 47%) |
| Opioids | Pain intensity–VAS | Opioids vs. placebo (3 RCTs) | Moderate | Significant effect in favor of opioids (MD = -16.73; 95% CI, -24.12 to -9.33; $I^2$ = 0%) |

**Table B. Summary of strength of evidence for the effectiveness of parenteral interventions for acute migraine versus placebo or an active treatment (Key Question 1) (continued)**

| Intervention | Outcome | Comparison (# of Studies) | SOE | Summary |
|---|---|---|---|---|
| Triptans | Headache relief at 60 min | Sumatriptan vs. placebo (4 RCTs) | Moderate | Significant effect in favor of sumatriptan (RR = 3.03; 95% CI, 2.59 to 3.54; $I^2$ = 0%) |
| | Headache relief at 120 min | Sumatriptan vs. placebo (4 RCTs) | Moderate | Significant effect in favor of sumatriptan (RR = 2.61; 95% CI, 2.09 to 3.26; $I^2$ = 21%) |
| | Headache relief at 30 min–VAS | Sumatriptan vs. placebo (2 RCTs) | Moderate | Significant effect in favor of sumatriptan (RR = -15.45; 95% CI, -19.49 to -11.41; $I^2$ = 0%) |
| | Pain-free status | Sumatriptan vs. placebo (5 RCTs) | Moderate | Significant effect in favor of sumatriptan (RR = 4.73; 95% CI, 3.77 to 5.94; $I^2$ = 0%) |
| | Headache recurrence at 24 hr in the ED | Sumatriptan vs. placebo (4 RCTs) | Low | Significant effect in favor of sumatriptan (RR = 0.72; 95% CI, 0.57 to 0.90; $I^2$ = 23%) |
| $MgSO_4$ | Pain intensity–VAS | $MgSO_4$ vs. placebo (3 RCTs) | Moderate | Significant effect in favor of $MgSO_4$ (MD = -9.73; 95% CI, -16.75 to -2.72; $I^2$ = 0%) |
| | Headache recurrence | $MgSO_4$ vs. placebo (2 RCTs) | Low | No significant difference between groups (RR = 0.68; 95% CI, 0.29 to 1.63; $I^2$ = 78%) |
| Mixed-Treatment Analysis | Pain reduction–VAS | Mixed-treatment comparison (15 RCTs | Low | Combination therapy: -41.3 mm (95% CI, -60.9 to -22.1)<br>Neuroleptics: -40.3 mm (95% CI, -49.0 to -31.7)<br>NSAIDs: -25.3 mm (95% CI, -38.8 to -12.0)<br>Opioids: -24.8 mm (95% CI, -35.7 to -14.2)<br>Metoclopramide : -23.9 mm (95% CI, -33.3 to -14.5)<br>DHE: -16.3 mm (95% CI, -32.6 to -0.6)<br>Orphan agents: -13.2 mm (95% CI, -23.6 to -2.7)<br>Sumatriptan: -12.3 mm (95% CI, -23.8 to -0.5)<br>Other antinauseants: -9.4 mm (95% CI, -29.2 to 11.1) |

CI = confidence interval (or credible interval in the case of mixed-treatment analysis); DHE = dihydroergotamine; ED = emergency department; MD = mean difference; $MgSO_4$ = magnesium sulfate; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence; VAS = visual analog scale

DHE was compared with other active treatments in five trials. Results were mixed for pain relief. Single trials compared DHE with meperidine, neuroleptic agents, sumatriptan, lidocaine, and lysine acetylsalicylic acid (insufficient SOE). The mixed-treatment analysis demonstrated that DHE monotherapy was similarly effective to orphan drugs and antinauseants, but less effective than opioids, NSAIDs, and metoclopramide for VAS-rated pain relief (low SOE).There was insufficient SOE for headache recurrence when comparing DHE with other active agents.

Triptans were compared with placebo in eight trials and with other active agents in six trials (Table B). Sumatriptan was more effective than placebo for pain relief (moderate SOE) and more effective than placebo for headache recurrence in the ED setting (low SOE). Single trials compared triptans with neuroleptics, metoclopramide, trimethobenzamide, DHE, and ketorolac, and results were mixed for pain relief (insufficient SOE). The mixed-treatment analysis demonstrated that sumatriptan was similarly effective to orphan agents but less effective than opioids, NSAIDs, and metoclopramide for VAS-rated pain relief (low SOE). There was insufficient SOE for headache recurrence when comparing triptans with other active agents.

$MgSO_4$ was compared with placebo in four trials and with other active agents in two trials (Table B). $MgSO_4$ was more effective than placebo for pain relief (moderate SOE). There was no difference between $MgSO_4$ and placebo for headache recurrence (low SOE). There was insufficient SOE for pain relief and headache recurrence when comparing $MgSO_4$ with other active agents.

Antihistamines were compared with placebo in one trial. There was insufficient SOE for pain relief.

Eight RCTs compared eight different combination interventions with other active agents. There was insufficient evidence to draw conclusions about the effectiveness of specific combination therapies for pain relief because single trials with low power investigated different pairs of interventions. The mixed-treatment analysis demonstrated that DHE in combination with metoclopramide or neuroleptic agents was one of the more effective treatment options for VAS-rated pain relief (low SOE).

### Key Question 2: Corticosteroids in the Prevention of Migraine Relapse

Seven trials assessed the effectiveness of dexamethasone compared with placebo in the prevention of migraine relapse (Table C). Patients receiving dexamethasone plus standard care were less likely to report recurrence of pain or headache up to 72 hours after discharge compared with placebo plus standard care (moderate SOE). The subgroups most likely to benefit from dexamethasone are discussed under KQs 5 and 6.

### Key Question 3: Adverse Effects

This question addressed the associated short-term adverse effects of the parenteral pharmacological interventions. We did not conduct a traditional pairwise meta-analysis of side effects because we did not identify multiple studies testing the same medications and reporting common side effects (insufficient SOE). We present a summary of adverse effects that provides an overall picture of which interventions had high rates of specific adverse effects. All of the reported side effects were considered minor and self-limiting. The results are presented by adverse effect categories (e.g., sedation, dizziness, vomiting). The frequency of side effects was examined for individual arms

**Table C. Summary of strength of evidence for corticosteroids in the prevention of migraine relapse (Key Question 2)**

| Outcome | Comparison (# Studies) | SOE | Summary |
|---|---|---|---|
| Headache recurrence (24–72 hr) | Dexamethasone vs. placebo (7 RCTs) | Moderate | Significant effect in favor of dexamethasone (RR = 0.68; 95% CI, 0.49 to 0.96; $I^2$ = 63%) |
| Headache recurrence (7 days) | Dexamethasone vs. placebo (1 RCT) | Insufficient | No significant difference between groups (RR = 0.70; 95% CI, 0.43 to 1.14) |
| Headache recurrence (30 days) | Dexamethasone vs. placebo (1 RCT) | Insufficient | No significant difference between groups (RR = 0.90; 95% CI, 0.58 to 1.41) |

CI = confidence interval; RCT = randomized controlled trial; RR = risk ratio; SOE = strength of evidence

of the trials and not as comparisons of effectiveness; the SOE was not graded.

### *General Findings by Intervention Class*

The main adverse effect of neuroleptic agents was akathisia symptoms; the odds of experiencing akathisia were about 10 times as great as with placebo. Similarly, the odds of experiencing akathisia following metoclopramide were 9.4 times as great as with placebo. Few short-term side effects were reported for NSAIDs. For patients receiving DHE, several side effects were reported; the most common were skin reactions (29 percent), local reactions (22 percent), sedation (20 percent), digestive issues (12 percent), nausea or vomiting (11 percent), and chest symptoms (9 percent). Few short-term side effects were reported for opioids. While the risk of dependence and the association with increased headache relapse are important long-term side effects, they were beyond the scope of this review. Short-term side effects were infrequent for patients receiving triptans. The most common side effect was local reaction (39 percent); this is not surprising, since these agents were all delivered subcutaneously. In patients receiving $MgSO_4$, high rates of skin flushing (10 percent) and local reactions (43 percent) were reported.

### *Vomiting*

Twenty-six studies reported on the rates of vomiting, nausea, and emesis. When participants took a placebo, the risk of vomiting or experiencing nausea and emesis was 11 percent (95% CI, 6 to 14 percent). The risk for active agents ranged from 3 percent (95% CI, 0 to 4 percent) to 57 percent (95% CI, 41 to 72 percent).

### *Sedation/Somnolence*

Twenty-five studies reported on the development of sedation/somnolence, including drowsiness and decreased levels of consciousness. The risk of developing sedation/somnolence as a result of taking a placebo was 5 percent (95% CI, 2 to 9 percent). The risk associated with active agents ranged from 3 percent (95% CI, 2 to 4 percent) to 84 percent (95% CI, 69 to 92 percent). The risk of experiencing sedation following administration of metoclopramide and prochlorperazine was 17 percent for each.

### *Dizziness*

Twenty-three studies reported dizziness as an adverse effect. Included in this category is postural hypertension, syncope, relative hypotension, orthostatic hypotension, fainting, head rushes, and dizzy spells. The risk of becoming dizzy in those who received a placebo was 5 percent (95% CI, 2 to 8 percent). The risk in those who received an active agent ranged from 2 percent (95% CI, 1 to 8 percent) to 80 percent (95% CI, 63 to 91 percent).

### *Local Reaction*

Fourteen studies measured local reactions, including pain or swelling at the injection site and IV site irritation. The risk in those who received placebo was 17 percent (95% CI, 11 to 22 percent). For those who were administered active agents, the risk ranged from 3 percent (95% CI, 0 to 6 percent) to 43 percent (95% CI, 16 to 75 percent).

### *Skin Reactions*

Ten studies measured skin reactions to the interventions administered, including skin flushing or rash. The risk in those who received placebo was 3 percent (95% CI, 1 to 6 percent). For those who were administered active agents, the risk ranged from 2 percent (95% CI, 1 to 8 percent) to 48 percent (95% CI, 28 to 68 percent).

### *Extrapyramidal Symptoms*

Seven studies reported extrapyramidal symptoms as a result of treatment. Included in this category are dystonic reactions, stiff neck, abnormal movements, and/or muscle twitching. Results for akathisia were examined in KQ 4. The risk in those who received placebo was 1 percent (95% CI, 0 to 4 percent). When participants were administered active agents, the risk ranged from 1 percent (95% CI, 0 to 4 percent) to 11 percent (95% CI, 0 to 22 percent).

### *Other Adverse Effects*

Chest symptoms, anxiety, digestion issues, or emergence reactions (e.g., unpleasant dreams) were reported in less than six studies.

### Key Question 4: Akathisia

Akathisia is an adverse effect associated with the use of several effective acute migraine headache treatment options. While self-limited, this symptom complex creates patient discomfort and distress. Two studies examined the development of akathisia when either metoclopramide or phenothiazine was used with and without an anticholinergic agent. Neither trial found a statistically significant difference in the occurrence of akathisia (Table D).

We conducted a post hoc mixed-treatment analysis of 15 studies that reported akathisia symptoms as a side effect. The analysis showed that metoclopramide and

neuroleptics (e.g., prochlorperazine) are the antimigraine agents most likely to cause these symptoms. The odds of experiencing akathisia symptoms following administration of these drugs were in the range of 10 times as great as the odds with placebo. Although other agents were associated with akathisia in the mixed-treatment analysis, lack of precise diagnostic criteria may limit these results.

### Key Questions 5 and 6: Subpopulations

This review cannot comment on variability in response to antimigraine treatment due to sex, race, or duration of headache because included studies often did not report subgroups based on these variables. In one study where sex was reported as a subgroup, sex did not predict headache relapse (insufficient SOE).

In one trial, dexamethasone was less effective at preventing relapse in patients who had more residual pain at discharge (VAS scores >2) (insufficient SOE). In three trials, dexamethasone was more effective in patients with prolonged headaches (moderate SOE). In one published review,[26] the authors found that higher doses (≥15 mg) of IV dexamethasone were more effective than lower doses (<15 mg). These dose comparisons were repeated in this review and, while a similar trend was observed, the differences were not statistically significant.

## Summary and Discussion

This report provides a comprehensive synthesis of the comparative effectiveness of parenteral pharmacological interventions versus standard care, placebo, or an active agent in the treatment of acute migraine headaches in adults presenting to the ED or an equivalent setting. Generally, active interventions were more effective than placebo in relieving pain and reducing headache recurrence. In the mixed-treatment analysis of pain relief (VAS), there was a clear indication that combinations of antimigraine medications (i.e., DHE in combination with either neuroleptics or metoclopramide) and neuroleptic monotherapy outperformed other active agents. The pain relief data must be weighed carefully with the data on side effects, especially akathisia.

### Findings in Relationship to What Is Already Known

Clinicians treating acute migraine headaches use a wide variety of parenteral agents.[27] Research on practice patterns in adult patients with acute migraine headaches demonstrates considerable variation as well as the use of non-evidence–based treatments.[10,28] Consequently, this CER is timely.

This review provides a comprehensive and up-to-date appraisal of the available evidence, including evidence from placebo-controlled and head-to-head trials. Although there are published systematic reviews of DHE,[29] metoclopramide,[30] meperidine,[28] and systemic corticosteroids,[26] this CER contextualizes each class of medication vis-a-vis every other class of acute migraine therapeutics. To our knowledge, no mixed-treatment analyses have been published on this topic. While we did not conduct meta-analyses of adverse effects, the evidence that we present provides a comprehensive summary of adverse effects across studies and interventions for this patient population.

The methodological techniques of the current review are robust and comprehensive, which should help to inform clinical practice guidelines and clinical decisionmaking in the future.

### Applicability

The study populations included in this review were relatively homogeneous. Most patients were female, and the mean age was generally between 30 and 40 years. Few studies reported on race or ethnicity; however, race was not an inclusion or exclusion criterion for any of the trials. Therefore, it would appear that these results are

**Table D. Summary of strength of evidence for the development of akathisia with the addition of anticholinergics to metoclopramide and phenothiazine (Key Question 4)**

| Outcome | Comparison (# Studies) | SOE | Summary |
|---|---|---|---|
| Akathisia | Metoclopramide + anticholinergic vs. phenothiazine + anticholinergic (1 RCT) | Insufficient | No significant difference between groups (OR = 1.50; 95% CI, 0.24 to 9.52) |
| | Prochlorperazine + diphenhydramine vs. prochlorperazine (1 RCT) | Insufficient | No significant difference (OR = 0.46; 95% CI, 0.17 to 1.28) |

CI = confidence interval; OR = odds ratio; RCT = randomized controlled trial; SOE = strength of evidence

generalizable to most patients with acute migraine seen in similar EDs based on sex and age. Results may not apply to patients seen in EDs that serve more culturally diverse populations. It is unknown whether males respond differently than females to the interventions included in this review. Similarly, it is unknown whether the results of this review apply to older populations.

Headache severity on admission was reported in a variety of ways. In studies that reported a baseline VAS (mm), the mean scores ranged from 6.3 to 9.4, indicating moderate to severe headaches. In other studies, patients self-rated their headache as moderate or severe. Migraine headache was diagnosed using the International Headache Society criteria[31] in 61 percent of the studies; the remaining studies used other criteria (19 percent) or did not specify their criteria (20 percent). The median baseline headache severity (VAS = 8 mm) for studies that used other criteria or that did not specify their criteria was the same as for studies that used the International Headache Society criteria. The results of this review may be generalizable to patients who present to the ED for treatment of moderate to severe acute migraine headache that has not responded to simple analgesics and for whom IV agents are being contemplated.

The majority of trials took place in the ED (79 percent). For two comparisons, more than 50 percent of the studies were conducted in a non-ED setting (2 of 12 studies for NSAIDs versus placebo and 2 of 24 studies for $MgSO_4$ versus placebo). The results for these interventions may not be generalizable to the ED setting.

The majority of trials took place in the United States or Canada (75 percent). Of the six studies investigating $MgSO_4$, four took place in either Brazil or Turkey. Of the nine studies that examined NSAIDs, five took place outside North America. The results of these studies may not be generalizable to acute migraine patients in the United States.

### Limitations of the Existing Evidence

The strength of the evidence was insufficient for the majority of outcomes across the head-to-head drug comparisons. This is primarily due to single, relatively small trials comparing pairs of active treatments. Where there were multiple trials, the strength of the evidence was low to moderate. These low grades were driven by moderate risk of bias within individual studies and a lack of consistency across trials. Most of the lack of clarity arose from poor descriptions of the system of randomization and concealment of allocation; however, this may be a limitation of the reporting and not of the conduct.

There is a relatively small body of evidence for the parenteral treatment of acute migraine headache in the ED setting, and the evidence arises from small studies, usually from single centers. Consequently, unique features of the trials (e.g., dose of drug, addition of an anticholinergic) make comparisons difficult. In addition, the therapeutic versus subtherapeutic dosing variation may limit some comparisons. This results in infrequent pooling and unclear direction of effect. For example, although multiple studies investigated neuroleptic agents, use of different specific agents, doses, and comparators, as well as variable use of anticholinergic or antihistamine agents, make it difficult to draw conclusions about this class of drugs. Conversely, the corticosteroid data on relapse demonstrate the power of having consistent comparisons, since the results are robust, precise, consistent, and generalizable.

There was inconsistency in reporting of outcomes from the studies included in this review, which hampered efforts to provide metagraphs and pooled evidence summaries. In the case of the main primary outcome of pain relief, the reporting of VAS scores, complete relief, ordinal scales, and other methods limited the number of studies included in the pooled results and may have biased estimates of effect. The direction of this bias is difficult to estimate.

The lack of consistency in the reporting of adverse effects impaired our ability to examine the safety of these agents. For example, the definition of adverse effects, the timing of assessment, and the scoring method used varied across studies. Still, serious or unexpected adverse effects were uncommon.

A small number of studies and overall small sample sizes contributed to imprecision. The nonsignificant differences between treatment comparisons reflect these weaknesses and should not prompt conclusions related to equivalence. Equivalence claims would require considerably larger sample sizes and 95% CIs that do not include the minimal clinically important differences.

Mixed-treatment analyses make an inherent assumption that the direct and indirect evidence can be used to estimate the same parameter. We checked the data for inconsistency and found that the number of inconsistent nodes was small. Therefore, inconsistency was not a major concern. We also had categories, “active combination agents” and “orphan agents,” that do not distinguish between possible heterogeneous treatments within these groups.

In addition to the issues identified above, this CER has several limitations. Due to the small number of studies for each comparison, we were unable to formally assess the potential for publication bias. Nonetheless, a comprehensive search of the published and gray literature was conducted without restrictions on study design or language. Consequently, the risk of publication bias should be low. There is also the possibility of study selection bias. To address this, at least two independent reviewers identified potentially relevant studies, and the authors are confident that the studies that were excluded were done so for consistent and appropriate reasons. Our assessment of the methodological quality of study publications was performed independently using the risk-of-bias tool, and we did not contact authors to verify the methods used. Some studies may have been adequately conducted; however, the methods were poorly reported.

## Future Research

The following general recommendations for future research are based on the preceding discussion regarding the limitations of the current evidence.

- Since many of the trials demonstrated a benefit to treatment that exceeded placebo effect, placebo-controlled trials in this field should be replaced with comparative effectiveness research focusing on migraine-specific agents for the delivery of care.
- Since many clinicians provide combination agents when patients present with acute severe migraine headache, more efforts should be initiated to determine the effectiveness of combination agents compared with sequential administration of agents or monotherapy.
- Consensus on outcomes and outcome measures, including adverse effects, is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- Research in parenteral management of acute migraine is ongoing. Consequently, updating this review should be a priority within 5 years.
- Future RCTs should investigate important subpopulations who may differentially respond to migraine treatment. This includes subgroup analysis by sex, race or ethnicity, age (e.g., older age groups), and duration of headache.
- Many trials included in this review were small and conducted in a single center, which may have delayed the dissemination of evidence and knowledge more than necessary. A multicentered acute migraine headache collaboration or consortium in emergency medicine would be an efficient method to answer the remaining important questions. The results from this review support calls for well-powered multicenter trials using standardized methodologies.
- Future RCTs should seek to minimize risk of bias by blinding study participants and outcome assessors, adequately concealing allocation, and handling and reporting missing data appropriately.
- Trials should be designed and conducted to minimize bias where at all possible. Investigators may find tools such as the CONSORT statements[32] helpful in designing and reporting on RCTs.

## Conclusions

This report provides the most comprehensive synthesis to date of the comparative effectiveness of parenteral pharmacological interventions versus standard care, placebo, or an active treatment in the management of acute migraine headaches in adults presenting to the ED or an equivalent setting. Overall, there are several important conclusions from this work. First, many agents appear to be effective in the treatment of acute migraine headache when compared with placebo. Neuroleptic monotherapy and DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options for pain relief (VAS). Second, several treatments reported here provide insufficient evidence for continued use (e.g., lidocaine, anithistamines, sodium valproate). Third, systemic corticosteroids effectively prevent relapses, especially in patients with prolonged headaches. Finally, the list of adverse effects is extensive, albeit they vary among agents and classes of drugs. Overall, the effectiveness of therapies described here must be weighed against their side effects to derive a strategy for treating patients with this common disorder. While the evidence collated here is an important step, more research is required in order to identify the most effective and safest parenteral medication for acute migraine.

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## Full Report

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