Draft Comparative Effectiveness Review

Number XX

Acute Migraine Treatment in Emergency Settings

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Preface

The Agency for Healthcare Research and Quality (AHRQ) conducts the Effective Health Care Program as part of its mission to organize knowledge and make it available to inform decisions about health care. As part of the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Congress directed AHRQ to conduct and support research on the comparative outcomes, clinical effectiveness, and appropriateness of pharmaceuticals, devices, and health care services to meet the needs of Medicare, Medicaid, and the Children's Health Insurance Program (CHIP).

AHRQ has an established network of Evidence-based Practice Centers (EPCs) that produce Evidence Reports/Technology Assessments to assist public- and private-sector organizations in their efforts to improve the quality of health care. The EPCs now lend their expertise to the Effective Health Care Program by conducting comparative effectiveness reviews (CERs) of medications, devices, and other relevant interventions, including strategies for how these items and services can best be organized, managed, and delivered.

Systematic reviews are the building blocks underlying evidence-based practice; they focus attention on the strength and limits of evidence from research studies about the effectiveness and safety of a clinical intervention. In the context of developing recommendations for practice, systematic reviews are useful because they define the strengths and limits of the evidence, clarifying whether assertions about the value of the intervention are based on strong evidence from clinical studies. For more information about systematic reviews, see http://www.effectivehealthcare.ahrq.gov/reference/purpose.cfm

AHRQ expects that CERs will be helpful to health plans, providers, purchasers, government programs, and the health care system as a whole. In addition, AHRQ is committed to presenting information in different formats so that consumers who make decisions about their own and their family's health can benefit from the evidence.

Transparency and stakeholder input from are essential to the Effective Health Care Program. Please visit the Web site (http://www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an e-mail list to learn about new program products and opportunities for input. Comparative Effectiveness Reviews will be updated regularly. We welcome comments on this CER. They may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 540 Gaither Road, Rockville, MD 20850, or by e-mail to epc@ahrq.hhs.gov.

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Structured Abstract

Objectives: To compare the effectiveness and safety of parenteral pharmacological interventions to treat migraine headaches in adults visiting the emergency department (ED).

Data Sources: A librarian searched 10 electronic databases. Conference proceedings, clinical trials registers, and reference lists were searched.

Methods: Two reviewers independently selected studies, assessed methodological quality, extracted data, and graded the strength of evidence. Data were pooled using a random effects model. A mixed treatment analysis was performed for pain relief and akathisia.

Results: Nine classes of drugs were investigated in 69 controlled trials. Risk of bias was low for 30 percent of the trials and unclear for 58 percent. Active interventions were more effective than placebo for pain relief and headache recurrence.

Results for pain relief were inconsistent when comparing metoclopramide with active agents (8 trials). There was no significant difference between metoclopramide and active agents (2 trials) for headache recurrence. The risk of sedation was 17 percent. The odds of developing akathisia was 10 times greater than with placebo.

Neuroleptics were more effective than other active agents for pain relief (14 trials). There was no difference between neuroleptics and active agents for headache recurrence (3 trials). The risk of sedation was 17 percent. The odds of developing akathisia was 10 times greater than with placebo.

Results were mixed for NSAIDs compared with active agents for pain relief (5 trials). NSAIDs were more effective than placebo and similarly effective to opioids and metoclopramide in the mixed treatment analysis. There was insufficient evidence for headache recurrence (1 trial). Few short-term side effects were reported.

Results were mixed for opioids compared with active agents for pain relief (10 trials). Opioids were more effective than placebo and similarly effective to NSAIDs and metoclopramide in the mixed treatment analysis. There were few short-term side effects.

Results were inconsistent for dihydroergotamine (DHE) compared with other active agents for pain relief (2 trials). DHE was more effective for headache recurrence compared with sumatriptan. The most common short-term side effects were skin reactions, local reactions, and sedation.

Results were mixed for pain relief when triptans were compared with other active agents (6 trials). Sumatriptan was less effective than DHE for headache recurrence (1 trial). Short-term side effects were infrequent.

Based on the mixed treatment analysis, the most effective treatments were combination therapy (i.e., DHE added to either neuroleptics or metoclopramide) or neuroleptic monotherapy. The available evidence failed to identify variable responsiveness based on subgroups.

Migraine relapse can be prevented with intravenous systemic corticosteroids provided in the ED, particularly in patients with prolonged headaches (>72 hours).

Conclusion: Many agents are effective in the treatment of acute migraine headache when compared with placebo. Several treatments provide insufficient evidence for continued use. Systemic corticosteroids effectively prevent headache relapse, especially in patients with prolonged headaches. More research is required to identify the most effective parenteral treatments for patients with acute migraine.

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Executive Summary

The Effective Health 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. Ahrq.gov/reports/final.cfm

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, seven percent reported using an ED or urgent care center for treatment of severe headache within the previous 12 months.[7] In the U.S., headaches accounted for 2.1 million (2.2 percent) ED visits annually.[8] Migraine sufferers who use the ED often report multiple ED visits annually.[7]

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 to treat acute migraine are commonly used in EDs in the U.S.[9] Among the agents that are used to treat acute migraine 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 agents (NSAIDs), and opioids. The most common first line agents employed for migraine treatment include opioids; however, in more recent research studies metoclopramide and the phenothiazine prochlorperazine appear to be commonly used.[13-15] While alternative phenothiazines exist, prochlorperazine is usually preferred due to its more favorable side effect profile. Intravenous DHE and ketorolac are considered alternative agents to treat acute migraine. Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and headache relapse.[16] 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).

Scope and Key Questions

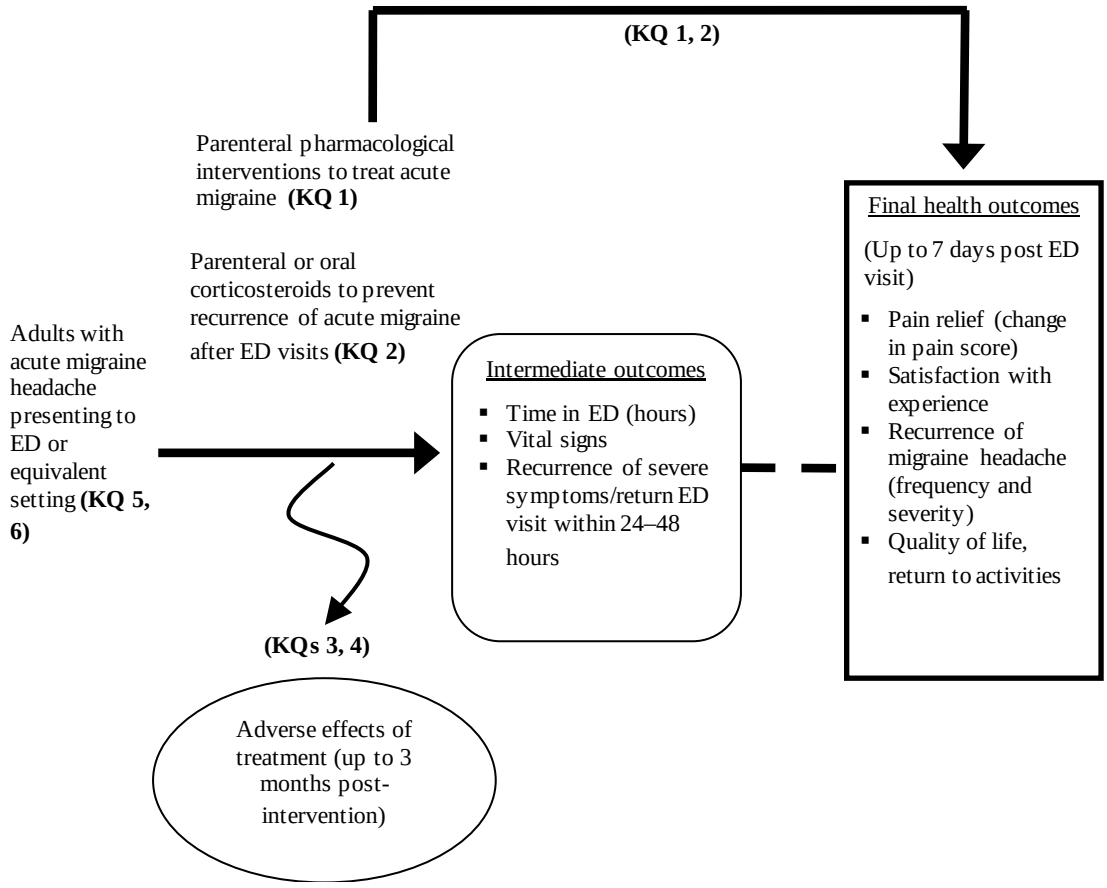
The first objective of this comparative effectiveness review (CER) is to assess the effectiveness of various parenteral medications for adult patients with moderate to severe acute migraine who present to an ED for treatment. The second objective is to assess important immediate and short-term side effects 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.

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. Does the effectiveness and safety of the parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and non-responders while in the ED?
6. Does 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 non-responders?

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 how parenteral pharmacological interventions and parenteral or oral corticosteroid interventions versus standard care, placebo, or an active comparator may result in intermediate outcomes such as time in ED, recurrence of severe symptoms, or return ED visits within 24–48 hours, and in 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 post-intervention.

Figure A: Analytic framework



KQ = Key Question; ED = emergency department.

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 XXXX 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 consultations with the Agency for Healthcare Research and Quality (AHRQ), the Scientific Resource Center, and a panel of key informants. AHRQ posted the KQs on their website for public comment for a period of 1 month. The EPC revised the KQs based on the public feedback, and AHRQ 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 June 2011. 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, WHO International Clinical Trials Registry Platform, and CenterWatch. U.S. Food and Drug Administration (FDA) 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. For first line ED treatment, eligible studies compared parenteral (IV, intramuscular, or subcutaneous) interventions with any agent used as 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 FDA reports, conference proceedings, and grey literature for potential relevance. The full text of articles identified as "include" or "unclear" by at least one reviewer were 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.

Decisions about how to group the different interventions were made in consultation with clinical experts. 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 versus metoclopramide). Combination therapies compared with an active comparator (e.g., metoclopramide plus DHE versus ketorolac) were considered 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 (e.g., prochlorperazine plus antihistamine versus metoclopramide was included in the neuroleptics versus metoclopramide category).

We reported adverse effects as they were reported by the authors of the study. For each adverse effect, the number of patients in each treatment, active comparator, or placebo group, and the number of patients with an adverse effect were recorded. 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 side effects was examined for individual arms of the trials, and not as comparative effectiveness comparisons.

Quality (Risk of Bias) Assessment

We assessed the internal validity of trials using the Cochrane Collaboration risk of bias tool.[17] 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. 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 pair-wise meta-analysis of adverse effects was not performed since we did not identify multiple studies with the same comparisons (e.g., prochlorperazine versus $MgSO_4$) that reported common adverse effects. Instead, we present a summary of drug related adverse effects by treatment arm which allows us to provide an overall picture of which interventions had a high risk of specific adverse effects. For each adverse effect category, risks were pooled using a random effects model to obtain a summary estimate and 95 percent CI.

For two outcomes, pain relief and akathisia, a mixed treatment analysis was conducted using a Bayesian network model to compare all interventions simultaneously.[33-35] Results are reported with 95 percent credibility intervals. We checked the analyses for consistency using cross validation of all contrasts that had direct evidence.[37]

Applicability

The applicability of the body of evidence was assessed following the PICOTS format used to assess study characteristics.[18] Factors that may potentially weaken the applicability of studies were reported in the results.

Grading the Body of Evidence

Two independent reviewers graded the body of evidence using the EPC GRADEapproach,[19] and resolved discrepancies by consensus. The key effectiveness outcomes for grading (KQs 1, 2, 5, 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.

Results

Description of Included Studies

The searches identified 2,136 citations from electronic databases. Screening based on titles and abstracts identified 205 potentially relevant studies. Hand searching identified 21 additional studies. There were 69 unique studies (67 RCTS, 2 NRCTs) that met the eligibility criteria.

The studies were published between 1986 and 2011. The majority were conducted in North America (76 percent). Sample sizes varied, with an overall median of 64 patients per study (interquartile range [IQR]: 40 to 100). For the majority of studies pain relief or severity was the primary outcome. Nine different classes of drugs were investigated. These are: antiemetics, neuroleptics, ergotamines, NSAIDs, opioids, corticosteroids, triptans, and a group of agents we collectively referred to as orphan agents (i.e., magnesium sulphate [$MgSO_4$], valproate).

Methodological Quality of Included Studies

Overall, 41 (59 percent) trials had an unclear risk of bias, 20 (30 percent) had low risk, and 8 (11 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.

Eleven 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

Metoclopramide was compared with placebo in six trials and with other active treatments in nine trials (Table A). Metoclopramide was significantly more effective than placebo for pain relief (moderate strength of evidence). There was insufficient evidence for headache recurrence. Results for pain relief were inconsistent when comparing metoclopramide monotherapy with other active treatments (excluding neuroleptics) (low strength of evidence). Metoclopramide was

generally less effective than neuroleptics for pain relief although this wasn't consistent across studies (low strength of evidence). The mixed treatment analysis demonstrated that as monotherapy, metoclopramide was similarly effective to opioids and NSAIDs for pain relief (low strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing metoclopramide with other active agents including neuroleptics.

Neuroleptics were compared with placebo in seven trials and with other active treatments in 17 trials (Table A). Neuroleptics were more effective than placebo for pain relief (moderate strength of evidence) and for headache recurrence (low strength of evidence). Neuroleptic agents were more effective than other active treatments for change in pain intensity (moderate strength of evidence). There was no significant difference between neuroleptics and active comparators with respect to headache recurrence (low strength of evidence).

NSAIDs were compared with placebo in two trials and with other active treatments in nine trials (Table A). NSAIDs were more effective than placebo for pain relief (moderate strength of evidence) and headache recurrence (low strength of evidence). Results were mixed for NSAIDs compared with other active agents for pain relief (low strength of evidence). NSAIDs were more effective than placebo and similarly effective to opioids and metoclopramide in the mixed treatment analysis (low strength of evidence). There was insufficient strength of evidence for headache recurrence when NSAIDs were compared with active agents.

Opioids were compared with placebo in three trials and to other active treatments in twelve trials (Table A). Opioids were more effective than placebo for pain relief (moderate strength of evidence). Results were mixed for opioids compared with other active agents for pain relief (low strength of evidence). Opioids were more effective than placebo and similarly effective to NSAIDs and metoclopramide in the mixed treatment analysis (low strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing opioids and other active agents.

DHE was compared with other active treatments in four trials (Table A). Results were mixed for pain relief (moderate strength of evidence). DHE was more effective in preventing headache recurrence compared with sumatriptan (low strength of evidence). The mixed treatment analysis demonstrated that as monotherapy, DHE was similarly effective to orphan drugs (drugs not easily classified and infrequently studied) and antiemetics, but less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence).

Triptans were compared with placebo in six trials (Table A). Sumatriptan was more effective than placebo for pain relief (moderate strength of evidence), and more effective than placebo for headache recurrence (low strength of evidence). Results for pain intensity were inconsistent across four trials that compared sumatriptan with other active agents (low strength of evidence). The mixed treatment analysis demonstrated that sumatriptan was similarly effective to orphan drugs yet less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence). In one RCT, sumatriptan was less effective than the active comparator for headache recurrence (low strength of evidence).

$MgSO_4$ was compared with placebo in three trials (Table A). There was no difference between $MgSO_4$ and placebo for pain relief (low strength of evidence). There was insufficient strength of evidence for headache recurrence. $MgSO_4$ was less effective for pain intensity when compared with other active agents in two RCTs (moderate strength of evidence).

Antihistamines were compared with placebo in one trial (Table A). There was insufficient strength of evidence for pain relief.

Eight RCTs compared eight different combination interventions with other active agents (Table A). There is insufficient evidence to draw conclusions about the effectiveness of specific combination therapies for pain relief. The mixed treatment analysis demonstrated that DHE in combination with metoclopramide or neuroleptic agents was one of the more effective treatment options (low strength of evidence).

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 B). 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 (RR = 0.68; 95% CI: 0.49, 0.96; $I^2 = 63\%$) plus standard care (moderate strength of evidence), especially in patients with prolonged headaches.

Key Question 3: Adverse effects

This question addressed the associated short-term adverse effects of the parenteral pharmacological interventions. All of the reported side effects were considered minor and self-limiting, and no major side effects were identified (e.g., death, stroke, disability). The results are presented by adverse effect categories (e.g., sedation, dizziness, vomiting). The frequency of side effects was examined for individual arms of the trials and not as comparative effectiveness comparisons. Therefore, strength of evidence was not graded.

Vomiting. There were 25 studies that reported on the rates of vomiting, nausea, and emesis. When participants took the placebo, the risk of vomiting or experiencing nausea and emesis was 11 percent (95% CI: 7 to 16 percent). The risk for active agents ranged from 3 percent (95% CI: 0 to 7 percent) to 57 percent (95% CI: 41 to 72 percent).

Sedation/somnolence. There were 24 studies that reported the development of sedation/somnolence including drowsiness and decreased levels of consciousness. The risk of developing sedation/somnolence as a result of taking placebo was 8 percent (95% CI: 3 to 12 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 common (17 percent for each).

Dizziness. Twenty-two 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 placebo was 4 percent (95% CI: 2 to 5 percent). The risk in those who received an active agent ranged from 2 percent (95% CI: 1 to 8 percent) to 32 percent (95% CI: 20 to 49 percent).

Local reaction. There were 13 studies that measured local reactions including pain or swelling at the injection site and IV site irritation. The risk in those who received placebo was 19 percent (95% CI: 13 to 24 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. There were nine studies that 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. Six 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 7 percent). When participants were administered active agents, the risk ranged from 1 percent (95% CI: 0 to 7 percent) to 11 percent (95% CI: 0 to 22 percent).

Other adverse effects. Chest symptoms, anxiety, digestion issues, emergence reactions (e.g. unpleasant dreams) were reported by less than six studies.

General findings by intervention class. The main side effect of neuroleptics was akathisia symptoms; the odds of experiencing akathisia was in the range of 10 times greater than with placebo and was similar to metoclopramide. There were few short-term side effects reported for NSAIDs or opioids. Side effects were commonly reported for patients receiving DHE. Short-term side effects were infrequent for patients receiving triptans. The most common side effect was local reaction (39 percent); however, 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.

Key Question 4: Akathisia

One study examined the differences in the development of akathisia when metoclopramide or phenothiazines were used with and without an anticholinergic agent. There was insufficient strength of evidence to draw a conclusion (Table C).

We conducted a post hoc mixed treatment analysis of 15 studies that reported akathisia as a side effect. In addition to neuroleptics and metoclopramide, other interventions included opioids, sumatriptan, and orphan drugs (drugs that did not fit into a unique class [i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide]). The only interventions that showed a statistically significant increase in akathisia were neuroleptic agents and metoclopramide. The odds of experiencing akathisia symptoms following administration of these drugs was in the range of 10 times greater than with placebo.

Key Question 5 and 6: Subpopulations

Overall, the evidence accumulated in this review did not identify specific subpopulations more likely to benefit from specific treatments. This group of studies rarely reported subgroups based on sex, race, and duration of headaches. In one study of relapse where sex was reported as a subgroup, variation in responses was not identified.

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 visiting the ED or an equivalent setting. Generally, active interventions compared with placebo were more effective in relieving pain and reducing headache recurrence. In the mixed treatment analysis of pain relief, there was a clear indication that combinations of anti-migraine medications (i.e., DHE in combination with either neuroleptics or metoclopramide) and neuroleptic monotherapy out-performed other agents. The pain relief data must be weighed carefully with the data on side effects, especially akathisia. The following is a summary of the evidence for the six KQs.

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

Outcome	Comparison (# studies)	Strength of Evidence	Summary
Metoclopramide			
Pain intensity–VAS	Metoclopramide vs. placebo (5 RCTs)	Moderate	Significant effect in favor of MET (MD = -21.88; 95% CI: -27.38, -16.38)
	Metoclopramide vs. neuroleptics (4 RCTs)	Low	Not pooled; inconsistent effect across studies
	Metoclopramide vs. other active agents (4 RCTs, 1 NRCT)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Metoclopramide vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.82; 95% CI 0.51, 1.32)
	Metoclopramide vs. neuroleptics (1 RCT)	Insufficient	No significant difference (RR = 0.41; 95% CI: 0.11, 1.51)
	Metoclopramide vs. other active agents (1 RCT)	Insufficient	No significant difference (RR = 0.82; 95% CI: 0.51, 1.33)
Neuroleptics			
Pain intensity–VAS	Neuroleptics vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (MD = -46.59; 95% CI: -54.87, -38.32, I^2 = 46%)
	Neuroleptics vs. other active agents (14 RCTs)	Moderate	Not pooled; statistical and clinical heterogeneity
Pain relief at 1 hr	Neuroleptics vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 3.21; 95% CI: 1.73, 5.95, I^2 = 75%)
Pain free at 1 hr	Neuroleptics vs. placebo (3 RCTs)	Moderate	Significant effect in favor of neuroleptics RR = 4.67; 95% CI: 2.13, 10.24, I^2 = 57%)
Headache recurrence	Neuroleptics vs. placebo (1 RCT)	Low	Significant effect in favor of neuroleptics (RR = 0.28; 95% CI: 0.15, 0.55)
	Neuroleptics vs. other active agents (3 RCTs)	Low	Not pooled; inconsistent effect across studies
NSAIDs			
Pain intensity–VAS	NSAIDs vs. other active agents (5 RCTs)	Low	Not pooled; inconsistent effect across studies
Pain free 1-2 hr	NSAIDs vs. placebo (2 RCTs)	Moderate	Significant effect in favor of NSAIDs (RR = 2.74; 95% CI: 1.26, 5.98)
	NSAIDs vs. other active agents (3 RCTs)	Low	Not pooled; inconsistent effect across studies
Pain response	NSAIDs vs. other active agents (4 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	NSAIDs vs. placebo (1 RCT)	Low	Significant effect in favor of NSAIDs (RR = 0.32; 95% CI: 0.17, 0.62)
	NSAIDs vs. other active agents (1 RCT)	Insufficient	No significant difference (RR = 1.5; 95% CI 0.28, 8.04)
Opioids			
Pain intensity–VAS	Opioids vs. placebo (3 RCTs)	Moderate	Significant effect in favor of opioids (MD = -16.73; 95% CI: -24.12, -9.33)
Pain intensity–VAS	Opioids vs. other active agents (10 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Opioids vs. other active agents (1RCT)	Insufficient	No significant difference (RR = 1.50; 95% CI: 0.28, 8.04)
DHE			
Pain intensity-VAS	DHE vs. other active agents (2 RCTs)	Low	Not pooled; inconsistent effect across studies
Pain relief at 2	DHE vs. other active	Low	Significant effect favoring sumatriptan

hrs	agents (1 RCT)		(RR = 0.86; 95% CI: 0.76,0.96)
Pain response	DHE vs. active agents (1RCT)	Low	Significant effect favoring NSAIDs (RR = 1.92; 95% CI: 1.10,3.36)
Headache recurrence	DHE vs. active agent (1 RCT)	Low	Significant effect favoring DHE (RR = 0.39; 95% CI: 0.26,0.59)
Triptans			
Headache relief at 60 min	Sumatriptan vs. placebo (3 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 3.06; 95% CI: 2.57, 3.65)
	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.47; 95% CI: 0.90, 2.38)
Pain free status	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 4.61; 95% CI: 3.62, 5.87)
	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.63; 95% CI: 0.85, 3.11)
Headache relief at 120 min	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 2.61; 95% CI: 2.09, 3.26)
	Almotriptan vs. placebo (1 RCT)	Low	Significant effect in favor of almotriptan (RR = 1.65; 95% CI: 1.15, 2.36)
Pain intensity	Sumatriptan vs. active agents (4 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Sumatriptan vs. placebo (4 RCTs)	Low	Significant effect in favor of sumatriptan (RR = 0.72; 95% CI: 0.57, 0.90)
	Sumatriptan vs. active agents (1 RCT)	Low	Significant effect in favor of DHE (RR = 0.39; 95% CI: 0.26, 0.59)
$MgSO_4$			
Pain intensity–VAS	$MgSO_4$ vs. placebo (2 RCTs)	Low	Not pooled; inconsistent effect across studies
	$MgSO_4$ vs. active agents (2 RCTs)	Moderate	Not pooled; results are consistent in favor of active agents
Pain reduction	$MgSO_4$ vs. placebo (2 RCTs)	Low	Not pooled; inconsistent effect across studies.
Headache recurrence	$MgSO_4$ vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.01; 95% CI: 0.66,1.54)
Antihistamines			
Pain intensity–VAS	Antihistamine vs. placebo (1 RCT)	Insufficient	No significant effect (MD = 10.40; 95% CI: -7.38, 28.18)
Combination therapy			
Pain intensity–VAS	DHE + MET or DHE + neuroleptics vs. placebo (3 RCTs)	Low	Significant effect in favor of combination therapy (MD = -41.3; 95% CI: -60.9, -22.1)

CI = confidence interval; MET = metoclopramide; MD = mean difference; MgSO4 = magnesium sulphate; RCT = randomized controlled trial; RR = risk ratio; SOE = Summary of Evidence; VAS = Visual Analogue Scale

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

Outcome	Comparison (# studies)	SOE	Summary
Headache recurrence (24–72 hr)	Corticosteroids vs. placebo (7 RCTs)	Moderate	Significant in favor of corticosteroids (RR = 0.68, 95% CI: 0.49, 0.96, I^2 = 63%)
Headache recurrence (7 days)	Corticosteroids vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.70; 95% CI: 0.43, 1.14)
Headache recurrence (30 days)	Corticosteroids vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.90; 95% CI: 0.58, 1.41)

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

Table C. 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 (OR = 1.50; 95% CI: 0.24, 9.52)

N = number; ROB = risk of bias

Findings in Relationship to What is Already Known

Clinicians treating acute migraine headaches use a wide variety of parenteral agents.[20] 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] Consequently, this comparative effectiveness review is timely.

This review provides the most comprehensive and up-to-date appraisal of the available evidence. This includes evidence from placebo controlled trials and head to head trials. Although there have been individual systematic reviews of DHE,[21] metoclopramide,[22] meperidine,[23] and systemic corticosteroids,[24] this review contextualizes each class of medication vis-à-vis every other class of acute migraine therapeutics. To our knowledge, there have been no mixed treatment analyses published regarding 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. This provides an overall picture of the interventions that had high rates of specific adverse effects.

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 homogenous. Most patients were female aged 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. Consequently, it would appear that these results are generalizable to most ED patients based on sex, race, and age. 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 severe headaches. In other studies, patients rated their headache as severe or moderate. The majority of studies took place in the ED. The results of this review should 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 parenteral agents are being contemplated.

Limitations of the Existing Evidence

The strength of the evidence was low or moderate for the majority of outcomes across the various drug comparisons. These low grades were driven by moderate risk of bias within individual studies and a lack of consistency among studies. 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 in 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 (e.g., dose of drug, addition of an anticholinergic) make comparisons difficult. This results in infrequent pooling and unclear direction. The best example of this is the neuroleptic agents where, over time, the exact agent varied, as did the dose, use of anticholinergic or antihistamine combinations, and other study design issues. 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 the outcomes from the studies included in this review, which hampered efforts to provide meta-graphs 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 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 the ability of the review 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. These observations limited the ability of the review to provide robust estimates of the risks associated with the agents. Side effects were examined for individual arms of the trials, and not as comparative effectiveness comparisons.

A small number of studies and overall small sample sizes contributed to imprecision. The non-significant differences between treatment comparisons reflect these weaknesses, and should not prompt conclusions about equivalence. Equivalence claims would require considerably larger sample sizes and 95 confidence intervals that did not include the minimally clinically important differences.

Mixed treatment analyses make an inherent assumption that the direct and indirect evidence estimate the same parameter. In our analyses we observed inconsistency that somewhat belies this assumption, and may cast some doubt on our results. We also had categories "active combination agents" and "orphan drugs" that do not distinguish between possible heterogeneous treatments within these groups.

In addition to the issues identified above, this comparative effectiveness review has several limitations. Due to the small number of studies for each comparison we were unable to formally assess potential for publication bias. Nonetheless, a comprehensive search of the published and grey 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 on study publications was performed independently using the risk of bias tool, and contact with authors to verify the methods used was not completed. 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:

- Future research 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. Authors may find tools such as the CONSORT statements[25] helpful in designing and reporting on randomized controlled trials.
- 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.
- Since many of the studies 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.
- There are several pressing areas where variation in management may be clarified in the near future, and updating this review should be a priority within 5 years.
- Many trials were small and conducted in a single center, delaying the dissemination of evidence and knowledge more than necessary. A multi-centered acute migraine headache collaboration or consortium in emergency medicine would be an efficient method to answer the remaining important questions.
- Future trials should investigate important subpopulations who may differentially respond to migraine treatment.
- Few studies reported any information regarding the costs of therapy. Since many of the agents reported in this review have long since been generic and, as a result, are inexpensive, the direct costs of care may not differ. Nonetheless, the variability in adverse effects, relapse, and lost time from life activities suggest that "cost" may be an important consideration to patients and society.
- The results for this review support calls for well powered multi-center studies using standardized methodologies.

Conclusions

This report provides the most comprehensive synthesis 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 or DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options. Second, several treatments reported here provide

insufficient evidence for continued use. 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, and perhaps cost, 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.

References and Included Studies

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med 2002;346(4):257-70. PMID:11807151

2. Bamford CC, Tepper SJ. Migraine – current understanding and treatment. Techniques Reg Anesth Pain Manage 2009;13(1):20-7.

3. Lipton RB, Hamelsky SW, Kolodner KB, et al. Migraine, quality of life, and depression: a population-based case-control study. Neurology 2000;55(5):629-35. PMID:10980724

4. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology 2010;74(8):628-35. PMID:20147658

5. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914. PMID:19861375

6. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. Arch Intern Med 1999;159(8):813-8.

7. Friedman BW, Serrano D, Reed M, et al. Use of the emergency department for severe headache. A population-based study. Headache 2009;49(1):21-30. PMID:19040677

8. Goldstein JN, Camargo CA, Jr., Pelletier AJ, et al. Headache in United States emergency departments: demographics, work-up and frequency of pathological diagnoses. Cephalalgia 2006;26(6):684-90. PMID:16686907

9. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med 2002;39(3):215-22. PMID:11867972

10. Colman I, Rothney A, Wright SC, et al. Use of narcotic analgesics in the emergency department treatment of migraine headache. Neurology 2004;62(10):1695-700. PMID:15159464

11. Richer LP, Laycock K, Millar K, et al. Treatment of children with migraine in emergency departments: national practice variation study. Pediatrics 2010;126(1):e150-e155. PMID:20530076

12. Richer L, Graham L, Klassen T, et al. Emergency department management of acute migraine in children in Canada: a practice variation study. Headache 2007;47(5):703-10. PMID:17501852

13. Innes GD, Macphail I, Dillon EC, et al. Dexamethasone prevents relapse after emergency department treatment of acute migraine: a randomized clinical trial. CJEM 1999;1(1):26-33. PMID:17659098

14. Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. Neurology 2007;69(22):2038-44. PMID:17942818

15. Rowe BH, Colman I, Edmonds ML, et al. Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. Headache 2008;48(3):333-40. PMID:18047499

16. Friedman BW. Migraine and other primary headache disorders. In: Rowe BH, ed. Evidence-based emergency medicine. 1st ed. Whiley-Blackwell; 2009:493-502.

17. Higgins JPT ADSJeobotCSMGatCBMG. Chapter 8: Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions Version 5 1 0 [updated March 2011]. 2011. Available from: URL: http://www.cochrane-handbook.org.

18. Atkins D, Chang SM, Gartlehner G, et al. Assessing applicability when comparing medical interventions: AHRQ and the Effective Health Care Program. J Clin Epidemiol 2011;64(11):1198-207.

19. Owens D, Lohr K, Atkins D. Grading the strength of a body of evidence when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program; AHRQ series paper 5. J Clin Epidemiol 2010;63(5):513-23. PMID:19595577

20. Vinson DR, Hurtado TR, Vandenberg JT, et al. Variations among emergency departments in the treatment of benign headache. Ann Emerg Med 2003;41(1):90-7. PMID:12514688

21. Colman I, Brown MD, Innes GD, et al. Parenteral dihydroergotamine for acute migraine headache: A systematic review of the literature. Ann Emerg Med 2005;45(4):393-401. PMID:15795718

22. Colman I, Brown MD, Innes GD, et al. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. BMJ 2004;329(7479):1369-73. PMID:15550401

23. Friedman BW, Kapoor A, Friedman MS, et al. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. Ann Emerg Med 2008;52(6):705-13. PMID:18632186

24. Colman I, Freidman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ 2008;336(7657):1359-61. PMID:18541610

25. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63(8):e1-37. PMID:20346624

Introduction

Background

Condition

Migraine is a chronic neurovascular disorder characterized by dysfunction of central and peripheral nociceptive pathways and intracranial vasculature.[1] The triggers of migraine headaches are multi-factorial; the pathophysiology is complex and incompletely understood. Migraines are thought to be initiated by stimulation and sensitization of the trigeminal peripheral nerves linked to intracranial vessels and meninges. If treatment is effective at this early stage, the migraine may be aborted and the symptoms may be less severe.[2] If treatment is ineffective, progression occurs through sensitization of central pain pathways leading to the thalamus.[3,4] Following central neuronal sensitization, cutaneous allodynia develops and headaches are more refractory to treatment.[5]

Migraine affects 12 percent of the general population in the United States.[6] Acute exacerbations of episodic and chronic migraine cause severe and disabling pain that may result in visits to an emergency department (ED) as well as decreased productivity and missed time from work, school, and other activities.[7] In the U.S., migraine and related medical issues result in costs of more than $13 billion per year due to lost productivity.[8] In Canada, this cost has been estimated at $3,025 per patient due to medical and indirect costs.[9]

Migraine has a negative impact on overall quality of life.[10] It is associated with psychiatric and medical comorbidities including major depressive disorder, bipolar disorder, anxiety and social phobias, cardiovascular risk,[11] and stroke.[12] Inadequate care of migraine is common: only 56 percent of migraine patients have been diagnosed correctly, and 49 percent use only over-the-counter rather than prescription medications to treat their headache.[6]

Diagnosis and Treatment

Migraine Headaches

Headaches may result from a variety of causes, some of which are benign and self-limiting while others are more serious. Once secondary causes of headache are excluded, migraine can be classified using criteria established by the International Headache Society.[13] An aura is a set of sensory symptoms which precede an impending headache, and include self-limited visual, tactile, and olfactory changes. A diagnosis of migraine headache can be made when the search for all malignant causes of headache has been exhausted and the patient meets the following criteria for migraine headache:

- Recurrent ($\geq$5 attacks in lifetime)
- Prolonged (lasting 4-72 hours)
- Associated with $\geq$2 of the following:
    - Unilateral location, pulsating quality
    - Moderate or severe pain intensity
    - Aggravated by or causing avoidance of routine physical activity
- Associated with >1 of the following:

- Nausea
- Vomiting
- Photophobia + Phonophobia/sonophonia

Chronic migraine is defined as headache on >15 days per month x 3 months.[13]

Acute Exacerbations and Emergency Department Presentation

Migraine causes acute headaches, which typically last 4 hours to 3 days if untreated and which frequently require bed rest, pain medications, and time off from work and other activities. Although most patients with migraine function normally between attacks, for many, migraine is a pervasive disorder that interferes with work, family, and social life.[1] Most individuals with migraine are able to treat their attacks at home; however, this treatment is not always successful. Of Americans with migraine, seven percent reported using an ED or urgent care center for treatment of severe headache within the previous 12 months.[14] In the U.S., headaches accounted for 2.2 percent of visits or 2.1 million ED visits per year.[15] Of patients who use an ED for treatment of migraine, 19 percent make multiple visits over the course of one year.[16]

While headache is a common cause of presentation to the ED, there is substantial practice variability among emergency clinicians in North America.[17-20] Twenty disparate parenteral agents to treat acute migraine are used in EDs in the U.S.[17] There is substantial variability across EDs. For example, dopamine antagonists are used in 60 percent of visits in some EDs compared with only 20 percent of visits in others.[19] Moreover, over-use of opioids has been observed in several studies.[17,18] Overall, there is a considerable gap between what is practiced in EDs and the evidence-based medical care, suggesting that a synthesis of this literature could lead to more standardized care.

Acute Migraine Management

Acute Headache Pain and Symptoms

Many agents are used to treat acute migraine, including 5-hydroxytryptamine (HT) receptor agonists (e.g., triptans), dopamine receptor antagonists (e.g., phenothiazines, metoclopramide, droperidol), ergot derivatives (e.g., dihydroergotamine [DHE]), intravenous nonsteroidal anti-inflammatory agents (NSAIDs), and opioids. While earlier studies have shown that opioids are commonly used,[17,18] the most common first line agents used for migraine treatment in more recent studies include metoclopramide and prochlorperazine, which is a phenothiazine.[21-23] Although alternative phenothiazines exist, prochlorperazine is preferred due to its relatively improved side effect profile. Intravenous DHE and ketorolac are considered alternative agents to treat acute migraine. Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and headache relapse.[16] A number of selective 5-HT_1 receptor agonists have been developed and represent a class of drugs called triptans. These agents are indicated for the acute treatment of migraine in adults; however, their use in many EDs is limited due to reduced efficacy with delayed administration,[24] the need for cardiac risk stratification prior to administration,[25] and frequent adverse events.[26] Finally, some physicians use agents sequentially (e.g., metoclopramide followed by ketorolac, if not fully recovered following in a 30-60 minute assessment period); however, the use of a combination treatment is also used (e.g., metoclopramide and ketorolac at the same time). Table 1 summarizes pharmacological

interventions that have been approved by the U.S. Food and Drug Administration; many of these are used off-label for acute migraine.

The first objective of this comparative effectiveness review (CER) is to assess the effectiveness of various parenteral medications for adult patients with acute migraine who come to an ED for treatment.

Side Effects

The second objective of this CER is to assess important immediate and short-term side effects of the different interventions. For example, opioids may be associated with drowsiness and impaired ability to function. Metoclopramide and the phenothiazines may cause akathisia and extrapyramidal side effects. This CER will examine the adverse effects caused by parenteral migraine therapies.

Prevention of Recurrence

Some patients with migraine suffer a short-term recurrence of headache after successful initial treatment that results in a return visit to a physician or ED. Research has shown that short-term or single-dose systemic corticosteroids, delivered intravenously (e.g., dexamethasone) or orally[27] prevent headache recurrence after treatment in an ED for acute migraine.[28] These agents are infrequently used,[29] however, and have important long-term side effects.[28] A third focus of this CER will be to examine the benefit and risk of using corticosteroids for preventing recurrence of acute migraine.

Table 1. Summary of pharmacological interventions for acute migraine

Generic name	Trade name(s)	Mode of administration
Agents for procedural sedation		
Ketamine	Ketalar	IV, IM
Ketofol	NA	IV
Propofol	Diprivan, Lusedra	IV
Anticonvulsant		
Magnesium sulfate	Magnesium sulfate	IV, IM
Valproic acid	Depacon	IV
Antiemetic		
Metoclopramide	Maxeran Reglan	IM 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 Solu-Medrol	IM IV, IM
Prednisolone	Prelone	Oral
Prednisone	Deltasone	Oral
Ergots		
Dihydroergotamine	DHE 45	IV, IM, SC
NSAID		
Ketorolac	Toradol	IV, IM
Opioids		
Butorphanol	Butorphanol tartrate	IV, IM
Buprenorphine	Buprenex	IM, IV
Fentanyl	Sublimaze	IM, IV
Hydromorphone	Dilaudid	SC, IM, IV
Meperidine	Demerol	IV, IM
Morphine	Apokyn Astramorph PF, DepoDur, Duramorph PF, Infumorph	SC IV
Nalbuphine	Nubain	SC, IM, IV
Neuroleptics		
Chlorpromazine	Largactil	IV, IM
Droperidol	Inapsine	IV, IM
Haloperidol	Haldol	IV*, IM
Prochlorperazine	Stematil (other modes available)	IV, IM
Triptan agents		
Sumatriptan	Alsuma, Imitrex (other modes available), Sumavel DosePro	SC
Other agents		
Promethazine	Phenergan	IV, IM

DHE = dihydroergotamine; IM = intramuscular; IV = intravenous; NA = not applicable; NSAID = non-steroidal anti-inflammatory drug; SC = subcutaneous

Scope and Key Questions

The objective of this report was to synthesize the available evidence on the comparative effectiveness of parenteral pharmacological interventions in the treatment of migraine and in the prevention of migraine relapse. The Key Questions (KQs) are as follows:

Key Question 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?

Key Question 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?

Key Question 3

What are the associated short-term adverse effects of these parenteral pharmacological interventions, and do they differ across interventions?

Key Question 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?

Key Question 5

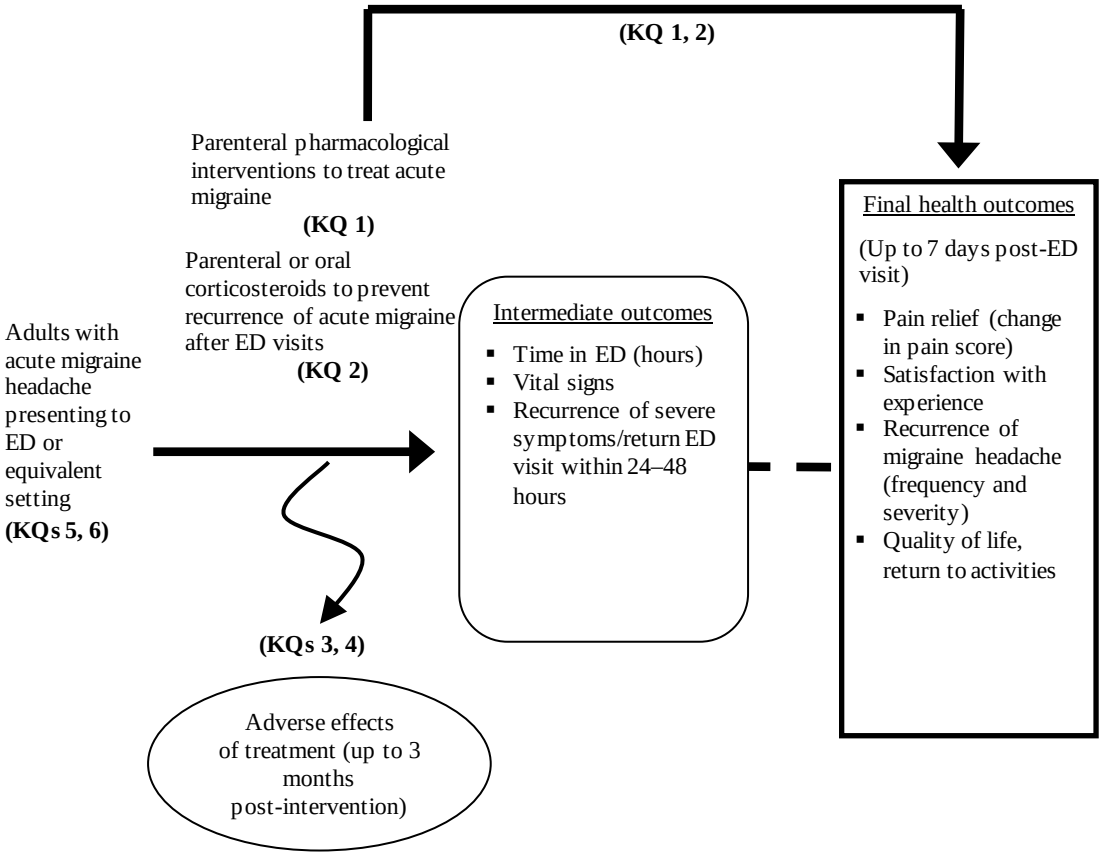
Does the effectiveness and safety of the parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and non-responders while in the ED?

Key Question 6

Does 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 non-responders?

Figure 1 provides an analytic framework to illustrate the population (P), interventions (I), control/comparison (C), and outcomes (O) that will 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 how parenteral pharmacological interventions and parenteral or oral corticosteroid interventions versus standard care, placebo, or an active comparator may result in intermediate outcomes such as time in ED, recurrence of severe symptoms, or return ED visits within 24–48 hours, and in 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 was received and were assessed up to 3 months post-intervention.

Figure 1: Analytic framework



KQ = Key Question; ED = emergency department.

Methods

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

Topic Refinement and Review Protocol

The XXXX 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 Key Questions (KQs) in consultation with the Agency for Healthcare Research and Quality (AHRQ), the Scientific Resource Center, and a panel of key informants. AHRQ posted the KQs on their website for public comment for a period of 1 month. The EPC revised the KQs based on the public feedback that was received, and AHRQ approved the final KQs.

A technical expert panel was assembled to provide content and methodological expertise throughout the development of the CER. The technical experts are identified in the front matter of this report.

Literature Search Strategy

A research librarian systematically searched the following bibliographic 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 June 2011. The search strategy did not employ any study design search filters, nor were language restrictions applied. See Appendix A for the detailed search strategies.

Search terms were selected by scanning search strategies of systematic reviews on similar topics and examining index terms of potentially relevant studies. The search terms were adapted to accommodate the controlled vocabulary and search languages of each database. Key search concepts and text words related to migraine, headache, emergency or acute care setting, and adults.

The 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, WHO International Clinical Trials Registry Platform, and CenterWatch. The U.S. Food and Drug Administration (FDA) 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 (from 2008 to 2011) were completed for the following scientific meetings that were identified by clinical experts: 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. As well, the Web sites of key organizations in emergency medicine, pain, headache, neuropharmacology, and

neurology were searched for relevant research. When necessary, study authors were contacted to obtain additional data or clarification.

Reference Manager© for Windows version 11.0 (2004–2005 Thomson ResearchSoft) bibliographic database was used to manage the results of all literature searches.

Inclusion and Exclusion Criteria

The eligibility criteria were developed in consultation with the technical expert panel and are provided in Table 2. The population of interest was adults ≥18 years of age with severe acute migraine headache presenting to an ED or equivalent setting. Studies that enrolled children or adolescents were included only when at least 80 percent of patients were ≥18 years of age, or when subgroup analyses for adult patients were provided. Studies that predominantly enrolled patients with non-migraine headaches (e.g., cluster headaches, tension headaches) were excluded. Studies that included a mixed cohort of patients with migraine and non-migraine headaches were included only if they reported data separately for migraine headaches or had a predominance of migraine headache patients. Studies that were excluded on the basis of population (i.e., headache type) were reviewed by a clinician (BHR).

Study Selection

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 FDA reports, conference proceedings, and grey literature for potential relevance. The full text of articles identified as "include" or "unclear" by at least one reviewer were retrieved. Finally, two reviewers independently assessed the full text of each study using a detailed form (Appendix B). Disagreements were resolved by consensus or third-party adjudication.

Table 2. Eligibility criteria for this review

Category	Criteria
Publication type	Primary research with no restriction on date and language
Study design	Clinical trials (RCTs and NRCTs) and cohort studies (prospective)
Population	Adult patients (≥18 years) with severe acute migraine headache presenting to an ED or equivalent setting and receiving parenteral therapy. Other headache terms we included were headache of benign etiology, (primary) vascular headache, crescendo-onset headache.
Intervention	**In-ED treatment:** First-line parenteral (intravenous/intramuscular/subcutaneous) interventions: a) Metoclopramide (Maxeran/Reglan) b) Dihydroergotamine c) NSAIDs (ketorolac [Toradol]) d) Phenothiazines (chlorpromazine [Largactil], prochlorperazine [Stematil], droperidol); e) Magnesium sulfate ($MgSO_4$) f) Triptan agents g) Meperidine (Demerol) h) Valproic acid i) Other agents: propafol (Diprivan), ketamine (Ketalar), opioids. **Prevention of relapse:** a) Parenteral corticosteroids (dexamethasone, others); b) Oral corticosteroids (prednisone, others) (Note:Corticosteroids must be used in addition to one of the parenteral interventions above)
Comparator	**In-ED treatment:** Any agent used as standard care, placebo, or an active comparator. Any route of administration **Prevention of relapse:** Standard parenteral therapy (i.e., one of the interventions listed above) plus placebo or no treatment
Outcomes of interest	1. Pain relief/change in pain score (measured either as a Visual Analog Score, a Likert scale of pain, or a 10-point verbal scale) 2. Complete elimination of pain prior to ED discharge 3. Vital signs (i.e., blood pressure, pulse) 4. Time in the ED (in minutes of total time and post-ED physician time). 5. Recurrence of headache (headache relieved in the ED and recurring within the following period) 6. Health services utilization (e.g., return visit to ED defined as an unscheduled visit for worsening symptoms) 7. Patient satisfaction with experience 8. Quality of life/return to activities **Adverse effects of intervention(s):** 1. Sedation/somnolence 2. Dizziness 3. Restless legs/akathisia 4. Anxiety 5. Vomiting 6. Chest symptoms, palpitations 7. Skin flushing 8. Other side effects There was no minimum followup duration requirement for inclusion.

ED = emergency department; NRCT = nonrandomized controlled trial; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial

Data Extraction

Data were extracted using a standardized, electronic form using Microsoft Excel™ 2007 (Microsoft Corp., Redmond, WA) (Appendix B). 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. The data extraction form was piloted tested on three studies, and revisions were made to address errors and inconsistencies among reviewers prior to proceeding with the remaining studies.

The following data were extracted: study and participant characteristics (including inclusion and exclusion criteria, age, sex, ethnicity, and diagnosis), intervention details (including dose, frequency, and duration), and outcomes including adverse effects. Information regarding the need for and use of rescue medications in the event of treatment failure was also extracted.

Outcome data were extracted only if quantitative data were presented or could be derived from graphs or figures. Outcomes that were only described qualitatively (i.e., statements that there was no difference between groups) were not included. Non-response was evaluated independently by two reviewers using two definitions: 1) non-response as defined by the authors; and 2) any patient who did not achieve complete resolution of pain (visual analogue score [VAS] = 0) before discharge or the end of the study. In cases where graphs were identified, they were enlarged and data were estimated by two people. In cases of abstracts and foreign language publications, non-response could not be adjudicated accurately.

Decisions about how to group the different interventions were made in consultation with clinical experts. For each drug class (e.g., neuroleptics), the intervention monotherapy is presented compared with placebo, followed by trials in which the intervention monotherapy is compared with another active treatment (e.g., neuroleptics versus metoclopramide). Combination therapies versus an active comparator (e.g., metoclopramide plus DHE versus ketorolac) were considered as a separate category. For the pain-related outcomes, drugs that were added to the pain intervention in order to specifically deal with side effects are grouped with the main drug class (e.g., prochlorperazine plus antihistamine versus metoclopramide was included in the neuroleptics versus metoclopramide category).

We reported drug related adverse effects as they were reported by the authors of the study. For each adverse effect, the number of patients in each treatment, active comparator, or placebo group, and the number of patients with an adverse effect were recorded. We counted each event as if it corresponded to a unique individual. Because an individual patient may have experienced more than one event during the course of the study, this assumption may have overestimated the number of patients that experienced an adverse effect. Only quantitative adverse effect data describing the number of patients who experienced an event were extracted; that is, studies that reported only p-values or reported one arm to have fewer events than another were not included in these analyses. The adverse effects of interest were determined a priori in with the consultation of the technical expert panel. The terminology used to describe adverse effect outcomes varied across studies. In consultation with our clinical experts, we classified adverse effects as outlined in Table 3.

Table 3. Adverse effects and associated terms

Adverse effect	Other terminology used in primary studies
Restlessness	Restless legs, akathisia, nervousness/tremulousness, jittery sensation
Sedation	Drowsiness plus sedation (in combination), drowsiness, decreased level of consciousness, somnolence
Dizziness	Postural hyptension, syncope, relative hypotension, orthostatic hypotension, fainting, head rush, dizzy spell
Anxiety	Mood change, moodiness
Chest symptoms	Palpitations
Skin flushing	Rash
Local reaction	Pain at injection site, swelling at injection site, IV site irritation
Digestion issues	Dyspepsia, heartburn, epigastric discomfort
Vomiting	Nausea, nausea plus vomiting (in combination)
Emergence reactions	Unpleasant dreams, nightmares
Extra-pyramidal symptoms	Dystonic reactions, stiff neck, stiffness or abnormal movements, muscle twitching
Other neurological adverse effects	Tingling, numbness, swelling sensation

IV = intravenous

Quality (Risk of Bias) Assessment of Individual Studies

We assessed the internal validity of randomized controlled trials (RCTs) and nonrandomized controlled trials (NRCTs) using the Cochrane Collaboration risk of bias tool (Appendix B).[30] This tool comprises six domains of potential bias (sequence generation, concealment of allocation, blinding, incomplete outcome data, selective outcome reporting, and "other" sources of bias). Each separate domain was rated as having "high," "low," or "unclear" risk of bias. Both blinding and incomplete outcome data were assessed separately for subjective outcomes (e.g., pain severity) and objective outcomes (e.g., blood pressure). For "other" sources of bias, baseline imbalances between groups, carryover in cross-over trials, and early stopping for benefit were assessed. In addition, the funding source for each study was extracted.

The overall assessment was based on the responses to individual domains. If one or more individual domains were assessed as having a high risk of bias, the overall score was rated as high risk of bias. The overall risk of bias was considered low only if all components were rated as having a low risk of bias. The risk of bias for all other studies was rated as unclear.

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 risk of bias tool and pilot tested on a sample of trials.

Data Analysis

The following assumptions were made and the following imputations were performed to transform reported data into the form required for analysis. Data from graphs were extracted using the measurement tool of Adobe Acrobat 9 Pro (Adobe Systems Inc., California, U.S.) when data were not reported in text or tables. If necessary, means were approximated by medians, and 95 percent confidence intervals (CI) were used to calculate approximate standard deviations. We calculated p-values when they were not reported. Change from baseline data was used wherever possible for continuous outcomes. As needed, change from baseline was calculated for studies that reported baseline and endpoint data, and a correlation of 0.5 was used to calculate the appropriate standard deviation.[31] Where change from baseline could not be

calculated, we used the reported endpoint data. One study[32] used a cross-over design; however, there was no washout period between administrations of the interventions, so only the first period data were used.

The majority of studies used the VAS scale. When pain scores were reported in any format other than VAS (mm), they were converted to VAS (mm) by multiplying results by a conversion factor. While using a standardized mean difference (SMD) is an alternative approach to dealing with varying scales across a single outcome, we chose this more direct conversion for two reasons. First, we believe that using VAS as a common scale would be less confusing than the "effect size" or SMD units of standard deviation. Second, since all pain scales used in the studies were subjective and numerical and anchored by severe and none (zero) extremes, a simple conversion to a 100 point scale was felt to be more consistent than a conversion using standard deviations when dealing with differences in pain among intervention groups.

For all studies, qualitative data are presented in the results section and in evidence tables. When appropriate, meta-analyses were performed to synthesize the available data. Studies were considered appropriate for pooled analyses if they were sufficiently similar in terms of their population, interventions, comparators, and outcomes.

The evidence for efficacy was summarized separately for each intervention category (e.g., neuroleptics, antiemetics). Within each intervention category, data are presented both by individual drug comparison and across the drug class (e.g., all neuroleptics).

A traditional pair-wise meta-analysis of adverse effects was not performed since we did not identify multiple studies with the same comparisons (e.g., prochlorperazine versus $MgSO_4$) that reported common adverse effects. Instead, we present a summary of adverse effects by treatment arm which allows us to provide an overall picture of which interventions had a high risk of specific adverse effects. For each adverse effect category, risks were pooled using a random effects model to obtain a summary estimate and 95 percent CI.

Review Manager Version 5.0 (The Cochrane Collaboration, Copenhagen, Denmark) was used to perform meta-analyses. For continuous variables, mean differences (MDs) were calculated for individual studies. For dichotomous outcomes, risk ratios (RR) or odds ratios (OR) were computed to estimate between-group differences. If no events were reported in one treatment arm, a correction factor of 0.5 was added to each cell of the two-by-two table in order to obtain estimates of the RR or OR. All results are reported with 95 percent CI. All meta-analyses used a random effects model. We quantified statistical heterogeneity using the I-squared (I^2) statistic.

Where there were more than 10 studies for the primary outcome (pain severity), a test for publication bias was visually performed using the funnel plot and quantitatively using the Egger graphical test.

For two outcomes, pain relief and akathisia, a mixed treatment analysis was conducted using a Bayesian network model to compare all interventions simultaneously and to use all available information on treatment effects in a single analysis.[33-35] The studies that were included in these analyses represented similar populations, outcomes, and designs, and the clinical heterogeneity was judged by the research team to be sufficiently low. MDs or log ORs were modeled using non-informative prior distributions. A normal prior distribution with mean 0 and large variance (10,000) was used for each of the trial means or log ORs, whereas their between study variance had a uniform prior with range 0 to 2 (akathisia) or 0 to 100 (pain score). These priors were checked for influence with sensitivity analyses. Markov Chain Monte Carlo simulations using

WinBugs software were carried out to obtain simultaneous estimates of all interventions compared with placebo, as well as estimates of which interventions were the best.[36] A burn-in sample of 20,000 iterations was followed by 200,000 iterations used to compute estimates. Results are reported with 95 percent credibility intervals. We checked the analyses for consistency using cross validation of all contrasts that had direct evidence.[37]

Applicability

Applicability of evidence distinguishes between *effectiveness* studies conducted in primary care settings that use less stringent eligibility criteria, assess health outcomes, and have longer followup periods than most *efficacy* studies.[38] The results of effectiveness studies are more applicable to the spectrum of patients in the community than efficacy studies, which usually involve highly selected populations. The applicability of the body of evidence was assessed following the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting) format used to assess study characteristics. Factors that may potentially weaken the applicability of studies were reported in the results.

Grading the Strength of a Body of Evidence

Two independent reviewers graded the strength of the evidence for key outcomes and comparisons using the EPC GRADE approach[39] and resolved discrepancies by consensus. For each key outcome, the following four major domains were assessed: risk of bias (rated as low, moderate, or high), consistency (rated as consistent, inconsistent, or unknown), directness (rated as direct or indirect), and precision (rated as precise or imprecise). No additional domains were used.

The key effectiveness outcomes for grading (KQs 1, 2, 5, 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. Based on the individual domains, the following overall evidence grades were assigned for each outcome for each comparison of interest: high, moderate, or low confidence that the evidence reflects the true effect. When no studies were available or where there were single studies with imprecise results, the strength of evidence was rated as insufficient.

To determine the overall strength of evidence score, the risk of bias domain was first considered. RCTs with a low risk of bias were initially considered to have a "high" strength of evidence, whereas RCTs with high or unknown risk of bias received an initial grade of "moderate" strength of evidence. The strength of evidence was then unchanged or downgraded depending on the assessments of that body of evidence on the consistency, directness, and precision domains.[39] In cases where results were not pooled, the overall strength of evidence rating was not downgraded.

Results

This chapter reports on the results of the literature search and evidence synthesis. First, the results of the literature searching, selection process, and a summary of the study characteristics and methodological quality of the included studies are described. The results of analyses are presented by Key Question (KQ). We present the results of the comparative effectiveness of parenteral pharmacological interventions versus placebo, standard care, or active agents (KQ 1 and KQ 2). These results are organized by drug class (e.g., neuroleptics, opioids) and then are grouped by placebo controlled studies or direct head-to-head comparisons of drugs or combinations of drugs. The adverse effect results (KQ 3) are organized by categories of adverse effects (e.g., sedation, nausea/vomiting) and then subgrouped by drug class. This is followed by results for the specific side effect, akathisia (KQ 4). Results related to subpopulations (KQ 5 and KQ 6) appear at the end of this chapter.

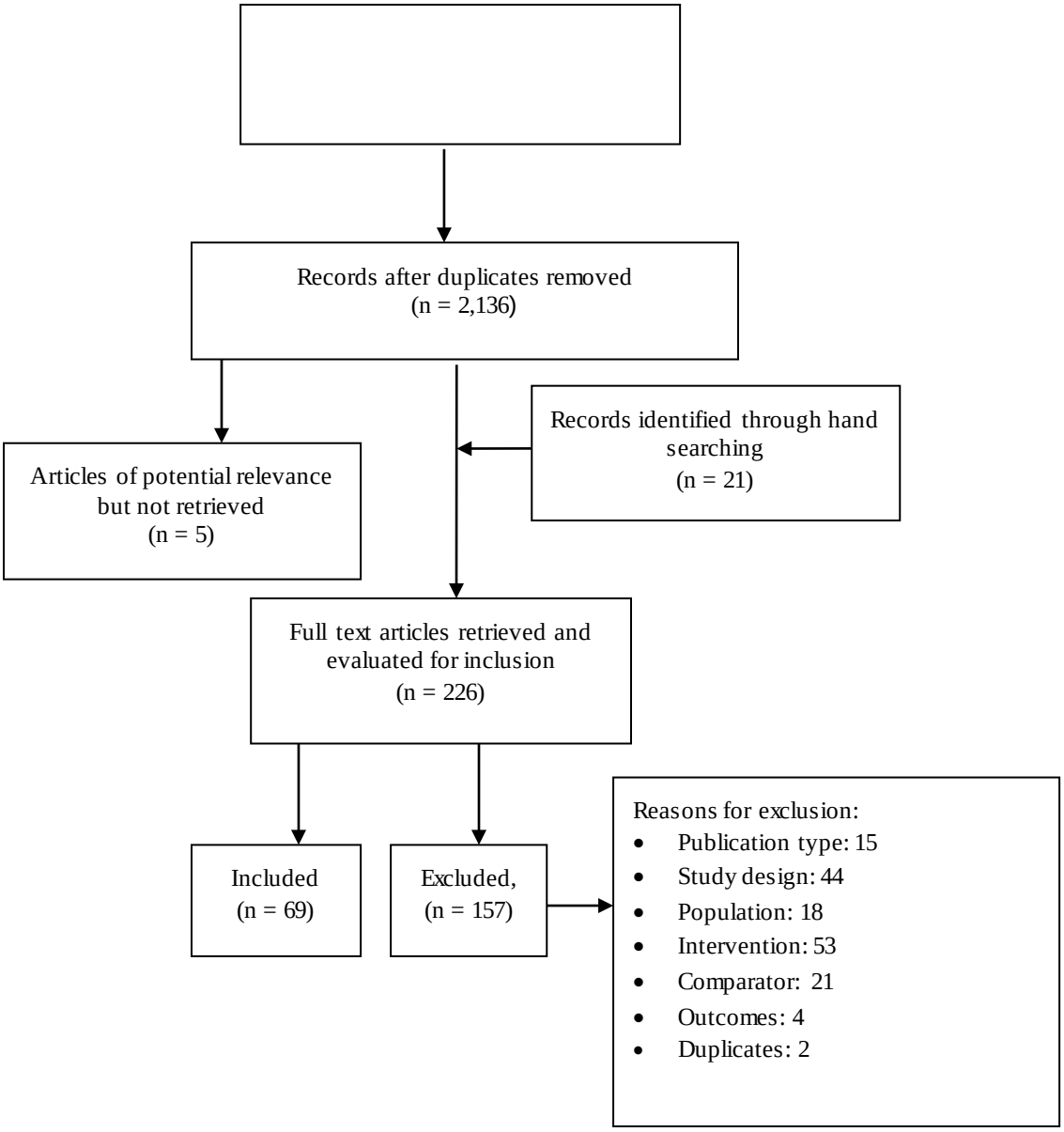
Metagraphs and tables reporting the strength of evidence for key outcomes are presented within each applicable section. Within each metagraph, the studies that provided data are indexed by the name of the first author and year of publication. A list of acronyms is provided at the end of the report.

Literature Search

The search identified 2,136 citations from electronic databases. Screening based on titles and abstracts identified 205 potentially relevant studies. Hand searching the reference lists from included studies, relevant systematic reviews, and conference proceedings identified 21 additional studies. The full text of five articles could not be retrieved through the university interlibrary loan service. Therefore, the full texts of 226 potentially relevant reports were evaluated for inclusion. Using a standardized inclusion–exclusion form (Appendix B), 69 studies were included, and 157 were excluded (Figure 2). Prospective cohort studies were screened for potential inclusion; however, none met the inclusion criteria. There are 67 randomized controlled trials (RCT) and 2 nonrandomized controlled trials (NRCT) in the review. Three studies were published in non-English language journals; these articles were translated and data were extracted by third party translators.

The most frequent reasons for study exclusion were: ineligible intervention (53), ineligible study design (44), and ineligible population (18). Forty-two studies were excluded for other reasons (Figure 2). A complete list of excluded studies and reasons for exclusion can be found in Appendix C.

Figure 2. Flow diagram of study retrieval and selection



Description of Included Studies

There were 69 unique studies that met the eligibility criteria. Evidence tables that describe the studies in more detail are presented in the results section. The studies were published between 1986 and 2011 (median = 2001 [interquartile range (IQR), 1993 to 2004]). The majority of studies were conducted in the U.S. (63 percent). The rest were conducted in Canada (13 percent), Turkey (9 percent), and other countries (15 percent). The most commonly reported measure of pain was the VAS. While there is no consensus on the minimally clinically important difference, a summary of the research suggests that a change in score between 1-2 cm (10-20 mm) on the VAS is considered clinically significant.[40-46]

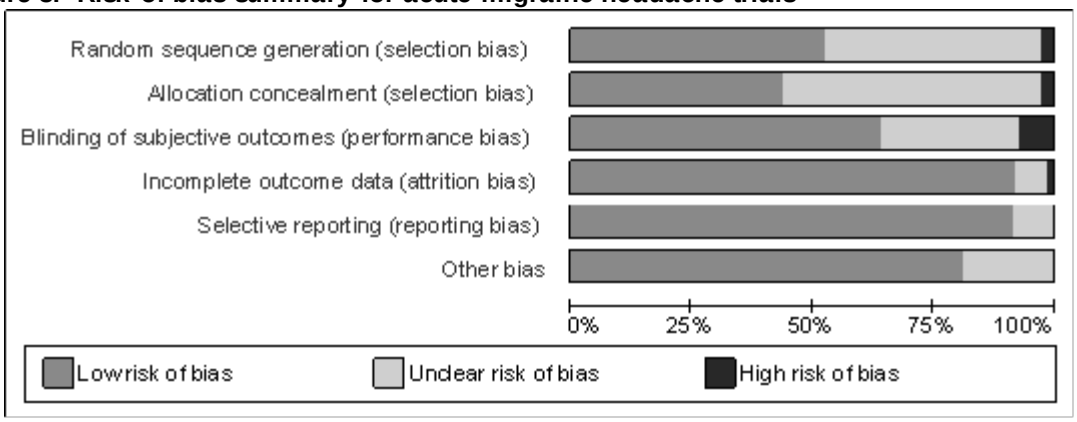
There were 67 RCTs and 2 NRCTs. Most trials were of parallel design; three used a cross-over design. Most trials (59, 86 percent) had two study arms. Seven trials (10 percent) had three study arms, and three (4 percent) had four study arms.

Methodological Quality of Included Studies

Risk of bias assessments are presented in Appendix D. A summary of the risk of bias for the 69 included studies is presented in Figure 3. Overall, 59 percent of the trials had an unclear risk of bias, 30 percent had low risk, and 11 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. Approximately 50 percent of studies were assessed as unclear risk of bias for sequence generation and allocation concealment.

Eleven studies were funded by industry,[47-57] seven were funded by associations and foundations,[21,22,58-62] one received government funding,[63] and two had other sources of funding.[64,65] Funding was not reported by 47 (68 percent) studies.[23,29,32,66-109]

Figure 3. Risk of bias summary for acute migraine headache trials



Key Question 1. Effectiveness of parenteral pharmacological interventions versus standard care, placebo or an active treatment

Sixty-nine trials reported the comparative effectiveness of parenteral pharmacological interventions compared with placebo, standard care, or an active treatment in the treatment of acute migraine headaches in adults visiting the emergency department (ED). The findings for Key Question (KQ) 1 are presented by drug class, comparing the drug class to placebo, if applicable, and then to other active agents. Note that some studies included both head-to-head and placebo comparisons and appear in both sections.

Antiemetics

Key Points

- Patients who received metoclopramide had greater improvement in pain intensity as measured by VAS (mm) compared with those on placebo based on five RCTs (moderate strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who received metoclopramide compared with placebo based on one RCT.
- Patients who received metoclopramide in combination (e.g., either with dihydroergotamine (DHE) or dexamethasone) had greater improvement in pain intensity compared with placebo based on one RCT (low strength of evidence).
- Results for improvement in pain intensity as measured by VAS (mm) were inconsistent for patients who received metoclopramide compared with those who received neuroleptics based on four RCTs (low strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who received metoclopramide compared with neuroleptics based on one RCT.
- Results for improvement in pain intensity as measured by VAS (mm) were inconsistent for patients who received metoclopramide compared with those taking other active agents based on four RCTs and 1 NRCT (low strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who received metoclopramide compared with magnesium sulphate ($MgSO_4$) based on one RCT.

Results

The results for the metoclopramide studies are summarized below. Table 4 and Table 5 and provide the strength of evidence grades for all key outcomes.

Antiemetics versus Placebo

Description of Included Studies

Six RCTs[78,86,87,90,104,110] assessed the effectiveness of the antiemetic metoclopramide compared with placebo. One three-armed trial[104] compared a combination of metoclopramide plus DHE with placebo and metoclopramide plus dexamethasone with placebo. The studies were all conducted in the ED. The mean ages of participant groups ranged from 32.1 to 40.0 years.

Participants were predominantly female, and no study reported the race or ethnicity of study participants. All studies reported pain relief or severity as the primary outcome. Timepoints measured in the ED ranged from 30 to 60 minutes. Post-ED followup timepoints ranged from 4 to 48 hours. In all but one study,[86] the secondary outcomes were adverse effects or ability to function. See Table 6 for details on study and patient characteristics.

Two studies had a low risk of bias;[78,86] the remaining four [87,90,104,110] had an unclear risk of bias (Appendix D).

Effectiveness Results

The detailed analyses of results are provided below. Results are presented by outcome. Studies in which metoclopramide monotherapy was compared with placebo are presented first, followed by studies in which metoclopramide was administered in combination with another drug and compared with placebo.

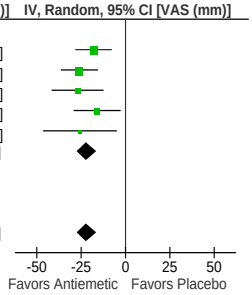
Metoclopramide monotherapy versus placebo

Five RCTs[78,86,87,90,110] assessed metoclopramide monotherapy compared with placebo.

Change in pain intensity (Visual Analogue Scale [VAS]). The change in pain intensity was measured by change in VAS (mm). The pooled results (Figure 4) showed that those who received metoclopramide experienced a statistically significant, homogeneous decrease in pain intensity compared with those who received placebo (MD = -21.88; 95% CI: -27.38, -16.38; I^2= 0%).

Figure 4. Change in pain intensity (VAS) in trials comparing metoclopramide and placebo

	Antiemetic			Placebo				Mean Difference	Mean Difference
Study or Subgroup	Mean [VAS (mm)]	SD [VAS (mm)]	Total	Mean [VAS (mm)]	SD [VAS (mm)]	Total	Weight	IV, Random, 95% CI [VAS (mm)]	IV, Random, 95% CI [VAS (mm)]
3.1.1 Metoclopramide versus Placebo									
Cete 2004	-40	25	37	-22	19	40	30.4%	-18.00 [-27.98, -8.02]	
Cicek 2004	13	21.6	50	39	28.9	48	29.5%	-26.00 [-36.13, -15.87]	
Coppola 1995	-42	24.65	22	-15	24.88	24	14.7%	-27.00 [-41.32, -12.68]	
Jones 1996	-29	24.88	28	-13	24.88	29	18.1%	-16.00 [-28.92, -3.08]	
Tek 1990	-48.67	40.5	24	-23	32.34	26	7.3%	-25.67 [-46.09, -5.25]	
Subtotal (95% CI)			**161**			**167**	**100.0%**	**-21.88 [-27.38, -16.38]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 4 (P = 0.62); I² = 0%									
Test for overall effect: Z = 7.80 (P < 0.00001)									
Total (95% CI)			**161**			**167**	**100.0%**	**-21.88 [-27.38, -16.38]**	
Heterogeneity: Tau² = 0.00; Chi² = 2.63, df = 4 (P = 0.62); I² = 0%									
Test for overall effect: Z = 7.80 (P < 0.00001)									
Test for subgroup differences: Not applicable									



VAS = visual analog scale

Relief of headache. One study[90] measured relief of headache using a questionnaire given to patients 1 hour after treatment. The difference in headache relief between the two groups was statistically significant in favor of the metoclopramide group (RR = 3.47; 95% CI: 1.50, 8.01).

Relief of nausea and vomiting. One study assessed the relief of nausea and vomiting[86] and reported that significantly more patients receiving metoclopramide experienced relief of nausea and vomiting compared with those who received placebo (RR = 4.19; 95% CI: 1.35, 13.03).

Headache recurrence. Patients in one study were contacted 24 hours after discharge from the ED to determine headache recurrence.[78] A lower proportion of patients who received

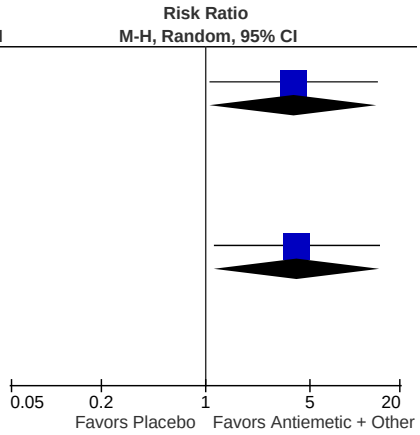
metoclopramide experienced recurrence of headache (16/37) compared with those who received placebo (21/40); however, the difference between groups was not statistically significant (RR = 0.82; 95% CI: 0.51, 1.32).

Metoclopramide in combination versus placebo

Pain improved by at least one unit. One study compared metoclopramide plus DHE and metoclopramide plus dexamethasone versus placebo.[104] Patients were asked to rate their headache on a scale from zero to three (three being the most severe headache). Comparisons of metoclopramide plus DHE versus placebo (RR = 3.89; 95% CI: 1.07, 14.10) and metoclopramide plus dexamethasone versus placebo (RR = 4.09; 95% CI: 1.15, 14.57) significantly favored the metoclopramide combination therapy (Figure 5).

Figure 5. Pain improved by at least one unit (four point scale) in trials comparing metoclopramide and placebo

Study or Subgroup	Antiemetic + Other agent Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
3.5.1 Metoclopramide + Dihydroergotamine versus Placebo						
Klapper 1986	7	9	2	10	100.0%	3.89 [1.07, 14.10]
Subtotal (95% CI)		**9**		**10**	**100.0%**	**3.89 [1.07, 14.10]**
Total events	7		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.07 (P = 0.04)						
3.5.2 Metoclopramide + Dexamethasone versus Placebo						
Klapper 1986	9	11	2	10	100.0%	4.09 [1.15, 14.57]
Subtotal (95% CI)		**11**		**10**	**100.0%**	**4.09 [1.15, 14.57]**
Total events	9		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.17 (P = 0.03)						

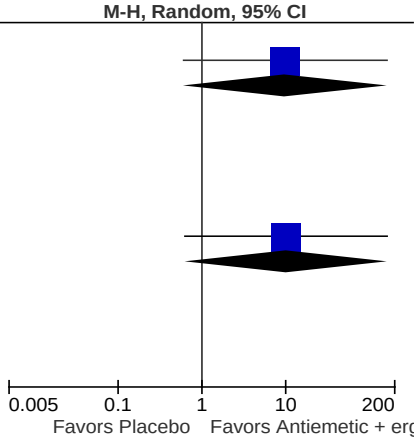


Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.96), I² = 0%

Return to normal functioning. In one study[104] patients were asked to rate their ability to function on a scale from zero (normal functioning) to three (requiring bed rest) 30 minutes after injection. More patients who were administered metoclopramide plus DHE improved their function compared with those who were given placebo (RR = 9.90; 95% CI: 0.61, 161.73). Similarly, more patients who were administered metoclopramide plus dexamethasone improved their ability to function compared with those who were administered placebo (RR = 10.08; 95% CI: 0.63, 162.06). The differences in both comparisons were not statistically significant (Figure 6).

Figure 6. Return to normal functioning (four point scale) in trials comparing metoclopramide and placebo

Study or Subgroup	Antiemetic + Ergot Events	Antiemetic + Ergot Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
3.6.1 Metoclopramide + Dihydroergotamine versus Placebo						
Klapper 1989	4	9	0	10	100.0%	9.90 [0.61, 161.73]
Subtotal (95% CI)		**9**		**10**	**100.0%**	**9.90 [0.61, 161.73]**
Total events	4		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.61 (P = 0.11)						
3.6.2 Metoclopramide + Dexamethasone versus Placebo						
Klapper 1989	5	11	0	10	100.0%	10.08 [0.63, 162.06]
Subtotal (95% CI)		**11**		**10**	**100.0%**	**10.08 [0.63, 162.06]**
Total events	5		0			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						



Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.99), I² = 0%

Table 4. Strength of evidence for metoclopramide versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Metoclopramide monotherapy vs. placebo	Pain intensity VAS (5; 328)	Moderate	Consistent	Direct	Precise	Moderate
	Headache recurrence (1; 77)	Low	Unknown	Direct	Imprecise	Insufficient
Metoclopramide+ DHE or dexamethasone vs. placebo	Pain improvement (1 RCT; 20)	Moderate	Unknown	Direct	Precise	Low

DHE = dihydroergotamine N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Antiemetics versus Active Agents

Description of Included Studies

Eight RCTs and 1 NRCT[59,70,74,77,78,86,87,101,110] assessed the effectiveness of metoclopramide with other active agents. Of these, four[59,70,86,87] specifically compared metoclopramide to neuroleptics. All interventions were delivered in the ED with timepoints measured between 30 and 120 minutes. Post-ED followup timepoints ranged from 4 to 48 hours. For all trials, the number of participants who were randomized ranged from 40 to 342 (median = 78; IQR = 70, 91). The mean ages of intervention groups ranged from 31.6 to 40.0 years. All of the studies had a pain related primary outcome (i.e., pain relief, change in pain intensity, pain free status). The secondary outcomes were varied and included adverse effects, time in ED, and use of rescue medication. See Table 6 for details on study and patient characteristics.

Four trials[59,74,78,86] had a low risk of bias, while five[70,77,87,101,110] had an unclear risk of bias (Appendix D).

Effectiveness Results

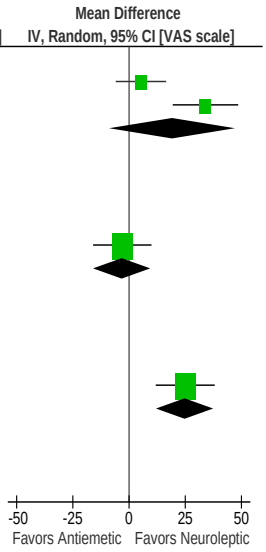
Antiemetics versus neuroleptics

Three studies[59,86,87] assessed metoclopramide monotherapy compared with neuroleptics (i.e., prochlorperazine and chlorpromazine). In one study, patients who received metoclopramide or prochlorperazine were also administered 25mg of IV diphenhydramine.[70]

Change in pain intensity (VAS). All four studies reported change in pain scores as measured on the VAS (mm) (Figure 7).[59,70,86,87] Results were inconsistent across studies. Two studies compared metoclopramide monotherapy with prochlorperazine.[59,87] While both studies favored the neuroleptic, only one study reported statistically significant results (MD = 34.0; 95% CI: 19.68, 48.32; I^2= 90%).[87] Statistically significant results favoring the neuroleptic were found in the one study comparing chlorpromazine to metoclopramide (MD = 25.0; 95% CI: 12.14, 37.86).[86] In the study where the antihistamine diphenhydramine was administered to both the metoclopramide and prochlorperazine groups, the differences in pain scores were not significant.[70]

Figure 7. Change in pain (VAS) in trials comparing metoclopramide and neuroleptics

Study or Subgroup	Antiemetic Mean [VAS scale]	Antiemetic SD [VAS scale]	Antiemetic Total	Neuroleptic Mean [VAS scale]	Neuroleptic SD [VAS scale]	Neuroleptic Total	Weight	Mean Difference IV, Random, 95% CI [VAS scale]
2.1.1 Metoclopramide versus Prochloperazine								
Cameron 1995	-43.4	28.5	44	-48.7	24.6	47	51.3%	5.30 [-5.67, 16.27]
Coppola 1995	-42	24.65	22	-76	24.88	24	48.7%	34.00 [19.68, 48.32]
Subtotal (95% CI)			**66**			**71**	**100.0%**	**19.27 [-8.85, 47.38]**
Heterogeneity: Tau² = 369.47; Chi² = 9.72, df = 1 (P = 0.002); I² = 90%								
Test for overall effect: Z = 1.34 (P = 0.18)								
2.1.2 Metoclopramide versus Prochloperazine + antihistamine								
Friedman 2008	52	29.88	38	55	27.08	39	100.0%	-3.00 [-15.75, 9.75]
Subtotal (95% CI)			**38**			**39**	**100.0%**	**-3.00 [-15.75, 9.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.46 (P = 0.64)								
2.1.3 Metoclopramide versus Chlorpromazine								
Jones 1996	-29	24.65	29	-54	24.88	28	100.0%	25.00 [12.14, 37.86]
Subtotal (95% CI)			**29**			**28**	**100.0%**	**25.00 [12.14, 37.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.81 (P = 0.0001)								



Test for subgroup differences: Chi² = 9.49, df = 2 (P = 0.009), I² = 78.9%

Severe headache recurrence. In one study,[59] patients were contacted by a nurse via telephone 48 hours post discharge to evaluate reucrrence of headache. Patients who received metoclopramide had less headache recurrence; however, the results were not statistically significant (RR = 0.41; 95% CI: 0.11, 1.51).

Relief of nausea and vomiting. One study[86] assessed relief of nausea and vomiting post treatment and found no statisically signicant difference between metoclopramide and prochlorperazine (RR = 0.71; 95% CI: 0.44, 1.16).

Additional outcomes. One study compared prochlorperazine and diphenhydramine versus metoclopramide and diphenhydramine.[70] The study assessed whether patients could sustain a pain free state (achieving a pain-free state within 2 hours of medication administration and maintaining it for 24 hours), sustained headache relief (for 24 hours), sustained normal

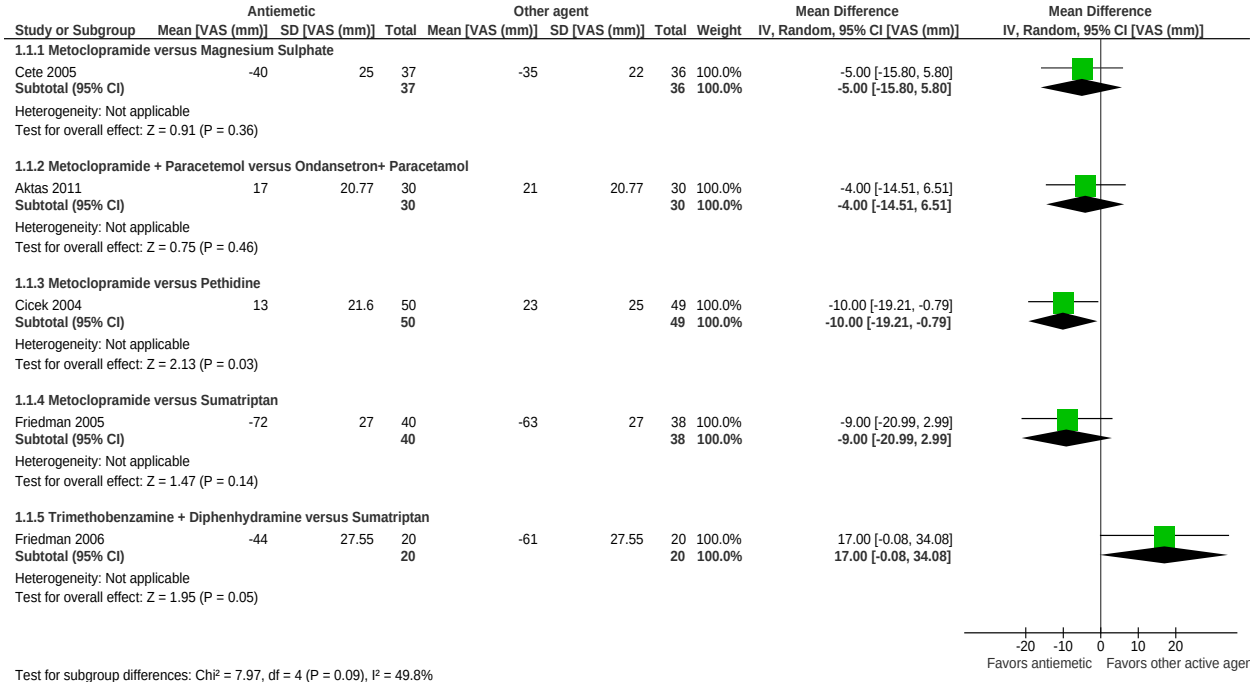
functioning, 2 hour pain free, and 2 hour headache relief. For every outcome measurement, the results were not statistically significant.

Antiemetics versus other active agents (excluding neuroleptics)

Four studies investigated the efficacy of metoclopramide compared with other active agents including: $MgSO_4$,[78] ondansetron plus paracetemol,[101] pethidine,[110] and sumatriptan.[77] In another study, trimethobenzamide plus diphenhydramine was compared with sumatriptan.[74]

Change in pain intensity (VAS). Five studies[74,77,78,101,110] measured pain or change in pain intensity using the VAS (mm) (Figure 8). Results were inconsistent across studies. While three studies reported nonsignificant pain or change in pain intensity,[74,78,101] one study reported a statistically significant difference favoring metoclopramide versus pethidine.[110] When metoclopramide was compared with sumatriptan, sumatriptan was more effective but the difference was not statistically significant.[77]

Figure 8. Change in pain intensity (<2 hours) (VAS) in trials comparing metoclopramide and other active agents (excluding neuroleptics)



Headache recurrence. One study measured headache recurrence at 24 hours and found no statistically significant difference between metoclopramide and $MgSO_4$[78] (RR = 0.82; 95% CI: 0.51, 1.33)

Other outcomes. One study assessed the administration of paracetemol with both metoclopramide and ondansetron.[101] The study measured the use of additional analgesia, mean duration of ED stay (minutes), and change in pain intensity at 24 hours (measured using a

numerical rating system). There were no statistically significant differences between groups for any of the outcomes.

There were no statistically significant differences in the single study of sumatriptan versus trimethobenzamine plus diphenhydramine in the measurement of pain free response at 1, 2, and 24 hours, or for headache response at 1 and 2 hours.[74] The same study assessed headache response at 24 hours, limitation to activities, and whether patients wanted the same medication in the future. There were no statistically significant differences for any of the outcomes.

Table 5. Strength of evidence for metoclopramide versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Metoclopramide vs. Neuroleptics	Pain intensity–VAS (4; 271)	Moderate	Inconsistent	Direct	Not pooled	Low
	Headache recurrence (1; 91)	Low	Unknown	Direct	Imprecise	Insufficient
Metoclopramide vs. other active agents	Pain intensity–VAS (5; 350)	Moderate	Inconsistent	Direct	Not pooled	Low
	Headache recurrence (1; 73)	Low	Unknown	Direct	Imprecise	Insufficient

N = number ; ROB = risk of bias; VAS = Visual Analogue Scale

Table 6. Patient and study characteristics of trials comparing metoclopramide with placebo or active agents

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Metoclopramide vs. placebo					
Cete, 2004, Turkey, RCT [78]	30min, (24 hr)	G1: MET, n=37, 10 mg IV G2: $MgSO_4$, n=36, 2 g IV P: Placebo, n=40, 100 mlIV	G1: 40 (13), 33 (89.2), NR G2: 40 (12), 27 (75.0), NR P: 40 (11), 35 (87.5), NR	G1: VAS: 73 mm (25), NR G2: VAS: 70 mm (22), NR P: VAS: 69 mm (19), NR	1: pain intensity at 30 min (VAS) 2: adverse reactions, need for rescue medication, recurrence at 24 hr
Cicek, 2004, Turkey, RCT [110]	45 min, (4 hr)	G1: MET, n=196 (Vascular headache); 140 (tension headache), IM Placebo + MET 10 mg IV G2: MET+PET, n=49, MET 10 mg IV+PET 50 mg IM G3: PET, n=49, IV Placebo+PET 50 mg IM P: Placebo, n=48, NR IV/IM	Total: 38.8 (11.1) vascular headache; 42.1 (13.8) for tension headache; mean age of all subjects 40.2 (12.4), 7.1 (female to male ratio for vascular headache), 2.5 (in tension headache group)	G1: NR, NR G2: NR, NR P: NR, NR	1: pain intensity (VAS) 2: side effects
Coppola, 1992, U.S., RCT [87]	30 min, (48hr)	G1: MET, n=24, 10mg IV G2: PCZ, n=22, 10mg IV P: placebo, n=24, NR IV	G1: NR, NR, NR G2: NR, NR, NR P: NR, NR, NR	G1: nonhatched VAS: 8.1, NR G2: nonhatched VAS:8.7, NR P: nonhatched VAS: 7.6, NR	1: median pain scores (nonhatched VAS) 2: median nausea scores, median sedation scores
Jones, 1996, U.S., RCT [86]	60 min (48 hr)	G1: PCZ, n=28, 10 mg IM G2: MET, n=29, 10 mg IM P: Placebo, n=29, 2 ml IM	Total: 32.1 (2.1), 63 (73.3), NR	G1: VAS: 8.1 (range 6-10), NR G2: VAS: 8.5 (range 7-10), NR P: VAS: 8.0 (range 6-10), NR	1: median pain scores (VAS) 2: nausea and vomiting
Klapper, 1989, U.S., RCT [104]	30 min, (24 hr)	G1: MET+DHE, n=11, 5-10mg MET and 0.75-1.0mg DHE IV G2: MET+DEX, n=9, 5-10mg MET IV, and 6mg DEX IV	G1: NR, NR, NR G2: NR, NR, NR P: NR, NR, NR	G1: NR, NR G2: NR, NR P: NR, NR	1: improvement by at least one unit (4-pt scale) 2: level of functioning (4-pt scale)

		P: Placebo, n=10, NR IV			
Tek, 1990, U.S., RCT[90]	60 min (48hr)	G1: MET, n=24, 10mg IV P: Placebo, n=26, 2 ml IV	G1: NR, NR, NR P: NR, NR, NR	G1: NR, NR P: NR, NR	1: mean relief score
Metoclopramide vs. neuroleptics					
Cameron, 1995, U.S., RCT [59]	45 min, (48hr)	G1: CPZ, n=47, 0.1mg/kg IV G2: MET, n=44, 0.1mg/kg IV	G1: Mean (range): 32.6(17-55), 38 (80.9), NR G2: Mean (range): 31.6(19-54), 35 (79.5), NR	G1: VAS: 7.15 cm; 38.9 hr G2: VAS: 7.76 cm; 47.2 hr	1: pain relief (VAS) 2: treatment failure , systolic blood pressure, headache recurrence
Coppola, 1992, U.S., RCT [87]	30 min, (48hr)	G1: MET, n=24, 10mg IV G2: PCZ, n=22, 10mg IV P: Placebo, n=24, NR IV	G1: NR, NR, NR G2: NR, NR, NR P: NR, NR, NR	G1: nonhatched VAS: 8.1, NR G2: nonhatched VAS:8.7, NR P: nonhatched VAS: 7.6, NR	1: median pain scores (nonhatched VAS) 2: median nausea scores, median sedation scores
Friedman, BW, 2008, U.S., RCT [70]	120 min, (24 hr)	G1: PCZ, n=39, 10 mg IV G2: MET, n=38, 20 mg IV (Both groups receive 25mg of DPH as well)	G1: 34 (10), 33 (84.6), Hispanic: 24 (61.5); Nonhispanic: 15 (38.5); White: 20 (51.3); Black: 35.9); Asian: 1 (2.6); Other: 4 (10.3) G2: 38 (12), 36 (94.7), Hispanic: 26 (68.4); Nonhispanic 12(31.6); White: 20 (52.3); Black: 16 (42.1); Asian: 0 (0.0); Other: 2 (5.3)	G1: 11-pt numerical rating scale: 8.4, 48 hr (median) G2: 11-pt numerical rating scale: 8.8, 72 hr (median)	1: change in pain intensity 2: sustained pain-free; sustained headache relief; sustained normal functioning; 2hr pain free; 2hr headache relief; rescue medication; adverse events; akathisia; drowsiness
Jones, 1996, U.S., RCT [86]	60 min (48 hr)	G1: PCZ, n=28, 10 mg IM G2: MET, n=29, 10 mg IM P: Placebo, n=29, 2 ml IM	Total: 32.1 (2.1), 63 (73.3), NR	G1: VAS: 8.1 (range 6-10), NR G2: VAS: 8.5 (range 7-10), NR P: VAS: 8.0 (range 6-10), NR	1: median pain scores (VAS) 2: nausea and vomiting
Antiemetic versus other active agents					
Aktas, 2011, Turkey, NRCT [101]	60 min, (NA)	G1: Ondansetron + Paracetamol, n=30, 4mg Ondansetron IV + 1g Paracetamol IV	G1: 35.3 (9.3), NR, NR G2: 37 (9.3), NR, NR	G1: NR, NR G2: NR, NR	1: pain severity (10-pt numeric rating scale; 0 is absence of pain, 10 is severe pain)

		G2: MET+ Paracetamol, n=30, 10mg MET IV+1g paracetamol IV			2: additional analgesia, mean durations of ED stay
Cete, Y, 2004, Turkey, RCT [78]	30min, (24 hr)	G1: MET, n=37, 10 mg IV G2: $MgSO_4$, n=36, 2 g IV P: Placebo, n=40, 100 mlIV	G1: 40 (13), 33 (89.2), NR G2: 40 (12), 27 (75.0), NR P: 40 (11), 35 (87.5), NR	G1: VAS: 73 mm (25), NR G2: VAS: 70 mm (22), NR P: VAS: 69 mm (19), NR	1: pain intensity at 30 min (VAS) 2: adverse reactions, rescue medication, recurrence at 24 hr
Cicek, 2004, Turkey, RCT [110]	45 min, (4 hr)	G1: MET, n=196 (Vascular headache); 140 (tension headache), IM placebo + MET 10 mg IV G2: MET+PET, n=49, MET 10 mg IV + PET 50 mg IM G3: PET, n=49, IV placebo + PET 50 mg IM P: Placebo, n=48, NR IV/IM	Total: 38.8 (11.1) vascular headache; 42.1 (13.8) for tension headache; mean age of all subjects 40.2 (12.4), 7.1 (female to male ratio for vascular headache), 2.5 (in tension headache group),	G1: NR, NR G2: NR, NR P: NR, NR	1: pain intensity (VAS) 2: side effects
Friedman, BW, 2005, U.S., RCT [77]	120 min, (24 hr)	G1: MET, n=40, 20 mg IV G2: SUM, n=38, 6 mg SC	G1: 34, 35 (87.5), Latino: 25 (62.5); Black: 12 (30.0; White: 2 (5.0) G2: 34, 32 (84.2), Latino: 24 (63.2); Black: 10 (26.3); White: 2 (5.3)	G1: NR, 32 hr G2: NR, 29 hr	1: change in NRS score 2: 24-hr pain score, pain-free headache response at 2 and 24 hr, need for rescue medication, adverse reactions
Friedman, BW, 2006, U.S., RCT [74]	ED discharge, (24 hr)	G1: TMB and DPH, n=20, TMB 200 mg SC + DPH 25 mg SC G2: SUM, n=20, 6mg SC	G1: 34 (9.7); 17 (85.0); Latino: 11 (55.0), Black: 8 (40.0), White: 1 (5.0) G2: 32 (8.9); 20 (100.0); Latino: 14 (70.0), Black: 5 (25.0), White: 0 (0.0)	G1: NR, 37 hr (SD: 24) G2: NR, 32 hr (SD: 36)	1: change in pain intensity between BL and 2 hr (11-point NRS for pain) 2: pain-free and headache response, pain intensity after 24 hr, rescue therapy, nausea, limitation to their usual daily activities, number of patients that wanted to receive the same medication

BL = baseline; CPZ = chlorpromazine; DEX = dexamethasone; DHE = dihydroergotamine; DPH = diphenhydramine; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; IM = intramuscular; IV = intravenous; MET = metoclopramide; $MgSO_4$ = magnesium sulphate; NR = not reported; NRCT = non randomized controlled trial; NRS = Numerical Rating Scale for Pain; P = placebo; PET = pethidine; PCZ = prochlorperazine; pt = point; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SUM = sumatriptan; TMB = trimethobenzamide; VAS = visual analogue scale

Neuroleptic Agents

Key Points

- Patients who received neuroleptics had greater improvement in pain intensity as measured by VAS (mm) compared with those receiving placebo based on four RCTs (moderate strength of evidence).
- Patients who received neuroleptics had greater pain relief at 1 hour compared with those receiving placebo based on 4 RCTs (moderate strength of evidence).
- Fewer patients who received neuroleptics experienced headache recurrence compared with those receiving placebo based on one RCT (low strength of evidence).
- Patients who received neuroleptics had greater improvement in pain intensity as measured by VAS (mm) compared with those receiving other active agents based on 14 RCTs (moderate strength of evidence).
- There was no difference in headache recurrence between patients who received neuroleptics compared with those receiving other active agents based on three RCTs (low strength of evidence).

Results

The results from studies that compared neuroleptics to placebo or to other active agents are presented below. Note that the studies that specifically administered neuroleptics versus metoclopramide were described previously in the antiemetic section. Table 7 and Table 8 provide the strength of evidence grades for all key outcomes.

Neuroleptic Agents versus Placebo

Description of Included Studies

Six RCTs[62,75,86,87,92,102] and one NRCT[85] evaluated the effectiveness of neuroleptics versus placebo. The neuroleptics included prochlorperazine,[62,85-87] chlorpromazine,[92,102] and haloperidol.[75] The trials all took place in the ED. The mean ages of the participant groups ranged from 29.6 and 36.0 years; age was not reported in one study.[87] In six studies, the majority of patients were female; in one study, 40 percent of the placebo group was female.[85] Race or ethnicity was not reported in any of the studies. The primary outcomes were pain related,[62,75,86,87,102] incidence of akathisia,[85] and response to treatment.[92] Secondary outcomes included therapeutic gain, nausea, vomiting, sedation cores, treatment failures, successful treatment response/therapeutic gain. The timepoints measured in the ED ranged from 30 minutes to 3 hours. The followup timepoints after discharge from the ED ranged from 24 hours to 1 month. Table 9 provides details on study and patient characteristics.

Two studies had a low risk of bias,[62,86] four[75,87,92,102] had an unclear risk of bias, and one[85] had a high risk of bias (Appendix D).

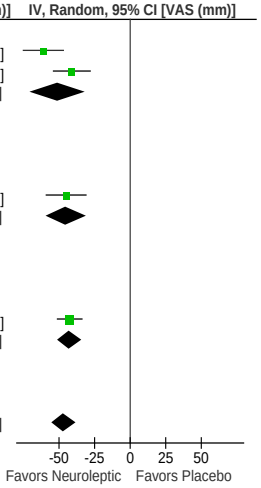
Effectiveness Results

Change in pain intensity (VAS). The change in pain intensity was reported by change in VAS (mm) (Figure 9). The pooled result of four studies was statistically significant MD = -46.59 (95% CI: -54.87, -38.32; I^2 = 46%).[75,86,87,102] In all but one study[102] authors reported pain as

change from baseline (negative numbers); when these data were not reported, final end of study data were presented (positive numbers).

Figure 9. Change in pain intensity (VAS) in trials comparing neuroleptics and placebo

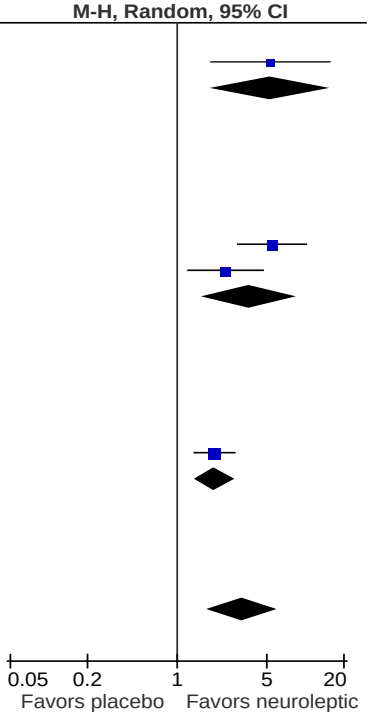
Study or Subgroup	Neuroleptic Mean [VAS (mm)]	Neuroleptic SD [VAS (mm)]	Neuroleptic Total	Placebo Mean [VAS (mm)]	Placebo SD [VAS (mm)]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [VAS (mm)]
2.1.1 Prochloperazine versus Placebo								
Coppola 1995	-76	24.88	24	-15	24.88	24	21.1%	-61.00 [-75.08, -46.92]
Jones 1996	-54	24.88	28	-13	24.88	29	23.4%	-41.00 [-53.92, -28.08]
Subtotal (95% CI)			**52**			**53**	**44.5%**	**-50.80 [-70.39, -31.20]**
Heterogeneity: Tau² = 152.48; Chi² = 4.21, df = 1 (P = 0.04); I² = 76%								
Test for overall effect: Z = 5.08 (P < 0.00001)								
2.1.2 Haloperidol versus Placebo								
Honkaniemi 2006	-54	17	20	-9	27	20	21.3%	-45.00 [-58.98, -31.02]
Subtotal (95% CI)			**20**			**20**	**21.3%**	**-45.00 [-58.98, -31.02]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 6.31 (P < 0.00001)								
2.1.3 Chlorpromazine versus Placebo								
Bigal 2002	10	24.88	68	52.5	24.88	60	34.2%	-42.50 [-51.14, -33.86]
Subtotal (95% CI)			**68**			**60**	**34.2%**	**-42.50 [-51.14, -33.86]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 9.64 (P < 0.00001)								
Total (95% CI)			**140**			**133**	**100.0%**	**-46.59 [-54.87, -38.32]**
Heterogeneity: Tau² = 32.77; Chi² = 5.58, df = 3 (P = 0.13); I² = 46%								
Test for overall effect: Z = 11.03 (P < 0.00001)								
Test for subgroup differences: Chi² = 0.60, df = 2 (P = 0.74), I² = 0%								



Relief of pain (1 hour). Four studies evaluated relief of headache at 1 hour (Figure 10).[62,75,92,102] All studies reported a statistically significant result in favor of the neuroleptics; the pooled result was RR = 3.21 (95% CI: 1.73, 5.95; I^2 = 75%). In two studies, the neuroleptic used was chlorpromazine.[92,102] In one study[102] patients were given an IV injection of 5.0ml/kg 0.9% normal saline solution followed by IV chlorpromazine, 0.1mg/kg diluted to 10 ml of 0.9% normal saline. In the second study, patients were administered 50mg/2ml of chlorpromazine.[92]

Figure 10. Relief of pain (1 hour) in trials comparing neuroleptics and placebo

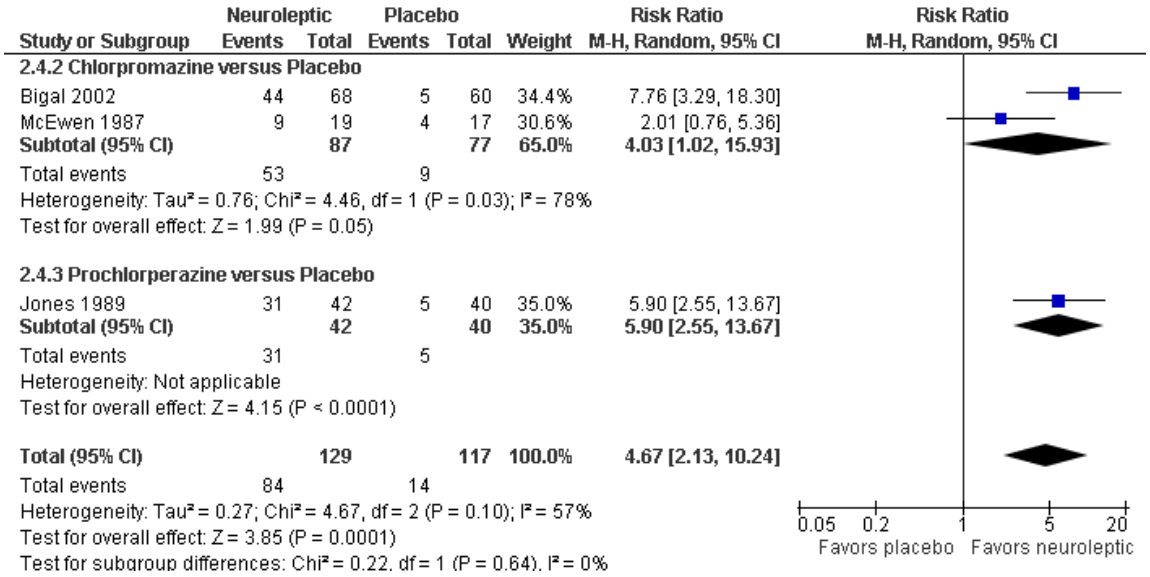
Study or Subgroup	Neuroleptic Events	Neuroleptic Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
2.2.1 Haloperidol versus Placebo						
Honkaniemi 2006	16	20	3	20	17.3%	5.33 [1.84, 15.49]
Subtotal (95% CI)		**20**		**20**	**17.3%**	**5.33 [1.84, 15.49]**
Total events	16		3			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.08 (P = 0.002)						
2.2.2 Chlorpromazine versus Placebo						
Bigal 2002	56	68	9	60	26.3%	5.49 [2.98, 10.13]
McEwen 1987	16	19	6	17	24.9%	2.39 [1.22, 4.67]
Subtotal (95% CI)		**87**		**77**	**51.2%**	**3.66 [1.56, 8.57]**
Total events	72		15			
Heterogeneity: Tau² = 0.27; Chi² = 3.51, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 2.99 (P = 0.003)						
2.2.3 Prochlorperazine versus Placebo						
Jones 1989	37	42	18	40	31.6%	1.96 [1.37, 2.81]
Subtotal (95% CI)		**42**		**40**	**31.6%**	**1.96 [1.37, 2.81]**
Total events	37		18			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.66 (P = 0.0003)						
Total (95% CI)		**149**		**137**	**100.0%**	**3.21 [1.73, 5.95]**
Total events	125		36			
Heterogeneity: Tau² = 0.28; Chi² = 11.79, df = 3 (P = 0.008); I² = 75%						
Test for overall effect: Z = 3.69 (P = 0.0002)						
Test for subgroup differences: Chi² = 4.30, df = 2 (P = 0.12), I² = 53.4%						



Relief of nausea and vomiting. One study assessed relief of nausea and vomiting 60 minutes after the administration of prochlorperazine or placebo.[86] Participants who received prochlorperazine experienced significantly greater relief than those who received placebo (RR = 5.89; 95% CI: 1.98, 17.57).

Pain free (1 hour). Three studies reported on pain free status of participants at 1 hour (Figure 11).[62,92,102] The pooled results of two studies[92,102] comparing chlorpromazine and placebo had statistically significant results favoring the neuroleptic (RR = 4.03; 95% CI: 1.02, 15.93; I^2 = 78%). The different concentrations of chlorpromazine may explain some of the heterogeneity. The pooled result of all three studies was statistically significant in favor of the neuroleptics (RR = 4.67; 95% CI: 2.13, 10.24; I^2 = 57%).

Figure 11. Pain free (1 hour) in trials comparing neuroleptics and placebo



Headache recurrence (24 hours). One study considered recurrence of pain to occur when patients stated that they were pain free any time after administration of the intervention, only to have the headache return within 24 hours.[102] Patients who received chlorpromazine had significantly lower rates of headache recurrence than those who were given placebo (RR = 0.28; 95% CI: 0.15, 0.55).

Patient satisfaction. One study reported patient dissatisfaction as the number of patients who asked for a second drug at the end of 1 hour.[92] We used the inverse of this number to determine patient satisfaction. Significantly more patients who received placebo asked for more medication compared with those who received chlorpromazine (RR= 3.28; 95% CI: 1.10, 9.82).

Akathisia. One NRCT found that significantly more patients (44 percent) in the prochlorperazine group reported "prochlorperazine induced akathisia at 1 hour" compared with no patients (0 percent) in the placebo group (RR = 36.13; 95% CI: 2.28, 572.89).[85]

Table 7. Strength of evidence for neuroleptics versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Neuroleptics vs. placebo	Pain intensity–VAS (4; 273)	Moderate	Consistent	Direct	Precise	Moderate
	Pain relief at 1 hr (4; 286)	Moderate	Consistent	Direct	Precise	Moderate
	Pain free at 1 hr (3; 246)	Moderate	Consistent	Direct	Not pooled	Moderate
	Headache recurrence (1;128)	Moderate	Unknown	Direct	Precise	Low

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Neuroleptic Agents versus Active Agents

Description of Included Studies

There were 17 RCTs[29,49,58,60,61,63-65,67-69,80,82-84,91,111] that assessed the effectiveness of neuroleptics versus other active agents. The neuroleptics included prochlorperazine,[29,58,63-65,67,69,82-84] chlorpromazine,[49,61,91] haloperidol,[111] droperidol,[80] methotrimeptrazine,[60] lidocaine,[91] and olanzapine.[68] One study was a three-arm trial comparing chlorpromazine, DHE, and lidocaine.[91] The active agents being compared included anticonvulsants (sodium valproate and $MgSO_4$),[63,84] corticosteroids (dexamethasone),[111] ergot (DHE),[91] neuroleptics (droperidol, prochlorperazine, lidocaine),[29,64,68,82,83,91] NSAIDs (ketorolac and ketorolac tropethamine),[49,65] opioids (meperidine),[60,61,80] somatostatin analog,[67] and triptans (sumatriptan).[58]

All studies took place in the ED with timepoints that ranged between 30 and 120 minutes. Post-ED followup ranged from 2 to 45 hours. Eight studies did not report any followup data after discharge from the ED.[58,63,65,68,69,80,83,84] The number of participants who were randomized ranged from 29 to 168 (median = 64; IQR: 40, 82). The mean age of patients in the intervention groups ranged from 27 to 34.6 years.

Every study but one had a pain related primary outcome. The one study measured akathisia as its primary outcome.[29] While the VAS was the primary means to measure pain, one study used the Wong-Baker Faces Rating Scale to assess mean pain scores.[49] Secondary outcomes varied among studies and included headache recurrence, patient satisfaction, nausea, and sedation.

Seven studies had low risk of bias,[29,49,58,60,63,83,84] nine had an unclear risk of bias,[61,64,65,67-69,80,82,111] and one had a high risk of bias[91] (Appendix D).

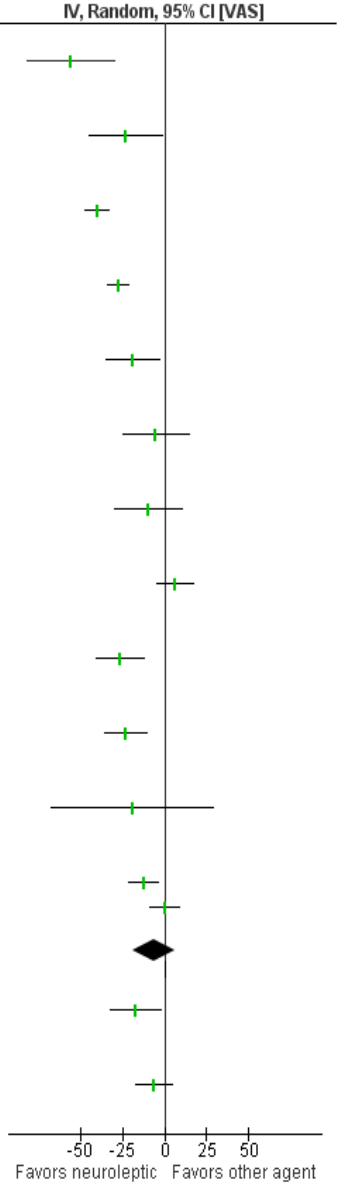
Effectiveness Results

Change in pain intensity (VAS). There were 14 studies that reported change in pain scores. Twelve studies specifically stated that pain was measured using the VAS (mm).[49,60,61,63,65,80,84,58,67-69,82] One reported using a headache scale ranging from 1 to 10,[91] while another used the Wong-Baker Faces Rating Scale.[49]

Eight studies[58,61,63,65,67,82,84,91] reported statistically significant results in favor of the neuroleptic (Figure 12). There were four studies in which the neuroleptic was favored over the other active agent, although the differences were not statistically significant.[49,68,69,80] In one study, the participants who received meperidine plus dimenhydrinate experienced more improvement in pain scores than those who received methotrimeptrazine; however, the difference was not statistically significant.[60] We did not pool the results due to statistical and clinical heterogeneity.

Figure 12. Change in pain (VAS) in trials comparing neuroleptics and active agents

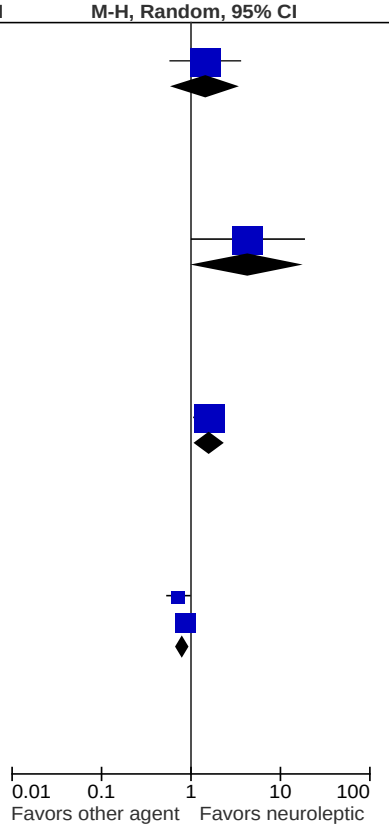
Study or Subgroup	Neuroleptic Mean [VAS]	Neuroleptic SD [VAS]	Neuroleptic Total	Other Agent Mean [VAS]	Other Agent SD [VAS]	Other Agent Total	Mean Difference IV, Random, 95% CI [VAS]
1.1.1 Prochlorperazine versus Sodium Valproate							
Tanen 2003	-64.5	30.58	20	-9	48.6	19	-55.50 [-81.14, -29.86]
1.1.2 Prochlorperazine versus Magnesium Sulphate							
Ginder 2000	-47	32.97	20	-24	32.97	16	-23.00 [-44.67, -1.33]
1.1.3 Chlorpromazine versus Dihydroergotamine							
Bell 1990	-67.5	10.27	24	-27.5	15.14	26	-40.00 [-47.12, -32.88]
1.1.4 Chlorpromazine versus Lidocaine							
Bell 1990	-67.5	10.27	24	-40	12.61	26	-27.50 [-33.85, -21.15]
1.1.5 Prochlorperazine versus Ketorolac							
Seim 1998	21	32	29	40	33	35	-19.00 [-34.97, -3.03]
1.1.6 Chlorpromazine hydrochloride versus Ketorolac tropethamine							
Shrestha 1996	-72	31	15	-66.7	23.2	15	-5.30 [-24.89, 14.29]
1.1.7 Droperidol versus Meperidine							
Richman 2002	-47	27.5	15	-37	27.5	14	-10.00 [-30.03, 10.03]
1.1.8 Methotrimeprazine versus Meperidine + Dimenhydrinate							
Stiell 1991	-40.3	22.7	37	-46.6	25.8	37	6.30 [-4.77, 17.37]
1.1.9 Chlorpromazine versus Meperidine + Dimenhydrinate							
Lane 1989	-70.6	21.8	24	-44.5	26.2	22	-26.10 [-40.10, -12.10]
1.1.10 Prochlorperazine + diphenhydramine versus Sumatriptan							
Kostic 2010	-73	25.85	31	-50	25.85	35	-23.00 [-35.50, -10.50]
1.1.11 Prochlorperazine versus Promethazine							
Callan 2008	-64.27	103	35	-45.22	103	35	-19.05 [-67.31, 29.21]
1.1.12 Prochlorperazine versus Droperidol							
Miner 2001	-28.9	33.1	86	-16.3	25.6	82	-12.60 [-21.52, -3.68]
Weaver 2004	-60	21.2	47	-60	21.2	48	0.00 [-8.53, 8.53]
Subtotal (95% CI)							**-6.23 [-18.58, 6.12]**
1.1.13 Prochlorperazine versus Octreotide							
Miller 2009	-50.5	20.42	20	-33.3	29.24	23	-17.20 [-32.13, -2.27]
1.1.14 Olanzapine versus Droperidol							
Hill 2008	29.7	16.77	45	35.9	32.4	42	-6.20 [-17.16, 4.76]



Headache relief. Headache relief was evaluated in four studies (Figure 13).[64,67,82,91] One of the trials had three study arms in which chlorpromazine, DHE, and lidocaine were compared.[91] In one study, significantly more participants in the octerotide group experienced headache relief compared with those in the prochlorperazine group (RR = 1.59; 95% CI: 1.08, 2.34).[67] In the two studies comparing prochlorperazine with droperidol, one study did not report a signifiant difference between groups,[64] while the other study showed a statistically significant difference favoring droperidol.[82]

Figure 13. Headache relief in trials comparing neuroleptics and active agents

Study or Subgroup	Neuroleptic Events	Neuroleptic Total	Other Agent Events	Other Agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 Chlorpromazine versus Dihyrdroergotamine						
Bell 1990	8	24	6	26	100.0%	1.44 [0.59, 3.56]
Subtotal (95% CI)		**24**		**26**	**100.0%**	**1.44 [0.59, 3.56]**
Total events	8		6			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.80 (P = 0.42)						
1.4.2 Chlorpromazine versus Lidocaine						
Bell 1990	8	24	2	26	100.0%	4.33 [1.02, 18.41]
Subtotal (95% CI)		**24**		**26**	**100.0%**	**4.33 [1.02, 18.41]**
Total events	8		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.99 (P = 0.05)						
1.4.3 Prochlorperazine versus Octreotide						
Miller 2009	18	20	13	23	100.0%	1.59 [1.08, 2.34]
Subtotal (95% CI)		**20**		**23**	**100.0%**	**1.59 [1.08, 2.34]**
Total events	18		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.36 (P = 0.02)						
1.4.4 Prochlorperazine versus Droperidol						
Miner 2001	38	86	50	82	36.5%	0.72 [0.54, 0.97]
Weaver 2004	34	47	40	48	63.5%	0.87 [0.70, 1.08]
Subtotal (95% CI)		**133**		**130**	**100.0%**	**0.81 [0.68, 0.98]**
Total events	72		90			
Heterogeneity: Tau² = 0.00; Chi² = 1.08, df = 1 (P = 0.30); I² = 8%						
Test for overall effect: Z = 2.22 (P = 0.03)						

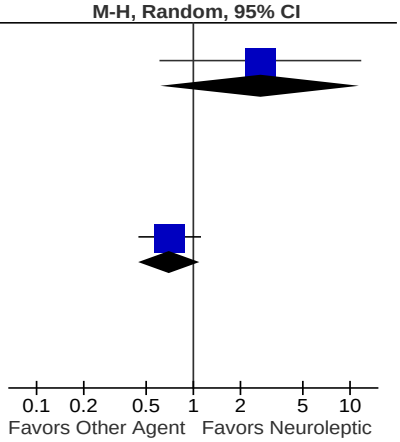


Test for subgroup differences: Chi² = 14.69, df = 3 (P = 0.002), I² = 79.6%

Pain free at 30 minutes. There were two studies that reported the number of patients who were pain free 30 minutes after administration of the interventions (Figure 14).[64,111] In one study, haloperidol was found to be more effective than dexamethasone,[111] while in the other study more people in the droperidol group were free from pain at 30 minutes than those in the prochlorperazine group.[64] Neither of these differences were statistically significant. At 120 minutes, haloperidol was signifantly more effective than dexamethasone (RR = 2.06; 95% CI: 1.21, 3.50) (metagraph not shown).[111]

Figure 14. Pain free at 30 minutes in trials comparing neuroleptics and active agents

Study or Subgroup	Neuroleptic Events	Neuroleptic Total	Other Agent Events	Other Agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.13.1 Haloperidol versus Dexamethasone						
Monzillo 2004	5	14	2	15	100.0%	2.68 [0.62, 11.64]
Subtotal (95% CI)		**14**		**15**	**100.0%**	**2.68 [0.62, 11.64]**
Total events	5		2			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.31 (P = 0.19)						
1.13.5 Prochlorperazine versus Droperidol						
Weaver 2004	18	47	26	48	100.0%	0.71 [0.45, 1.11]
Subtotal (95% CI)		**47**		**48**	**100.0%**	**0.71 [0.45, 1.11]**
Total events	18		26			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.52 (P = 0.13)						

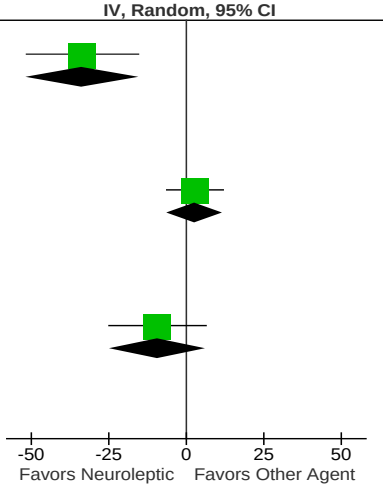


Test for subgroup differences: Chi² = 2.89, df = 1 (P = 0.09), I² = 65.4%

Nausea. Three studies assessed the effect of a neuroleptic versus another active agent on nausea as a symptom of migraine (Figure 15).[63,67,68] Only one study reported a statistically significant result in which the prochlorperazine group experienced a greater reduction in nausea than the sodium valproate group (MD = -33.5; 95% CI: -51.55, -15.45).[63]

Figure 15. Nausea in trials comparing neuroleptics and active agents

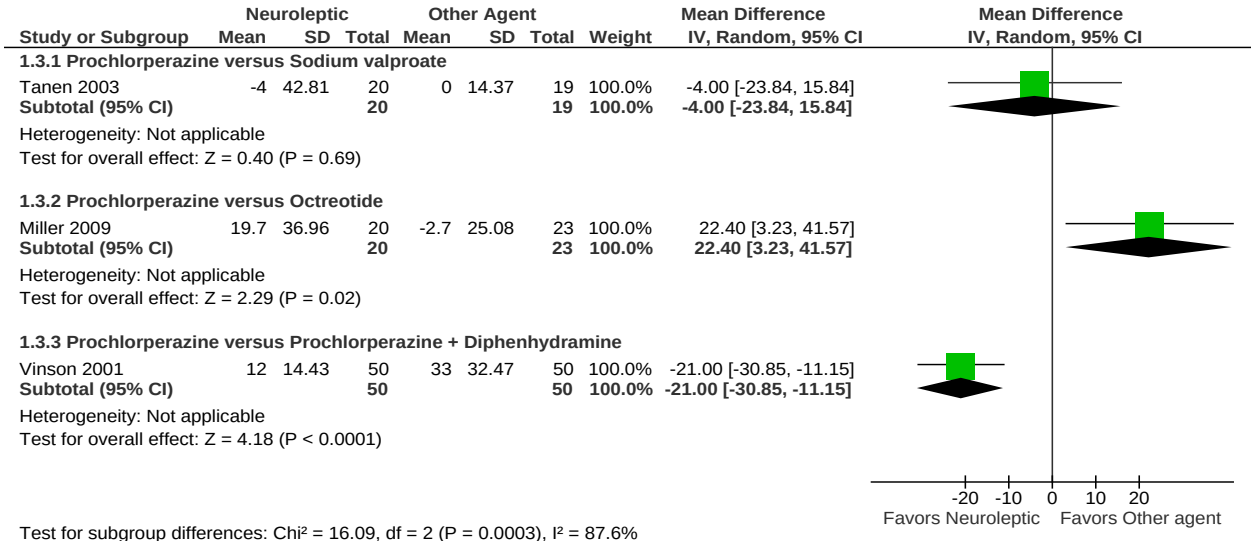
Study or Subgroup	Neuroleptic Mean	Neuroleptic SD	Neuroleptic Total	Other Agent Mean	Other Agent SD	Other Agent Total	Weight	Mean Difference IV, Random, 95% CI
1.2.1 Prochlorperazine versus sodium valproate								
Tanen 2003	-35.5	38.585	20	-2	14.03	19	100.0%	-33.50 [-51.55, -15.45]
Subtotal (95% CI)			**20**			**19**	**100.0%**	**-33.50 [-51.55, -15.45]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.64 (P = 0.0003)								
1.2.2 Olanzapine versus Droperidol								
Hill 2008	13.6	25.67	45	10.8	17.03	42	100.0%	2.80 [-6.30, 11.90]
Subtotal (95% CI)			**45**			**42**	**100.0%**	**2.80 [-6.30, 11.90]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
1.2.3 Prochlorperazine versus Octreotide								
Miller 2009	-36.6	27.27	20	-27.3	24.71	23	100.0%	-9.30 [-24.95, 6.35]
Subtotal (95% CI)			**20**			**23**	**100.0%**	**-9.30 [-24.95, 6.35]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.16 (P = 0.24)								



Test for subgroup differences: Chi² = 12.67, df = 2 (P = 0.002), I² = 84.2%

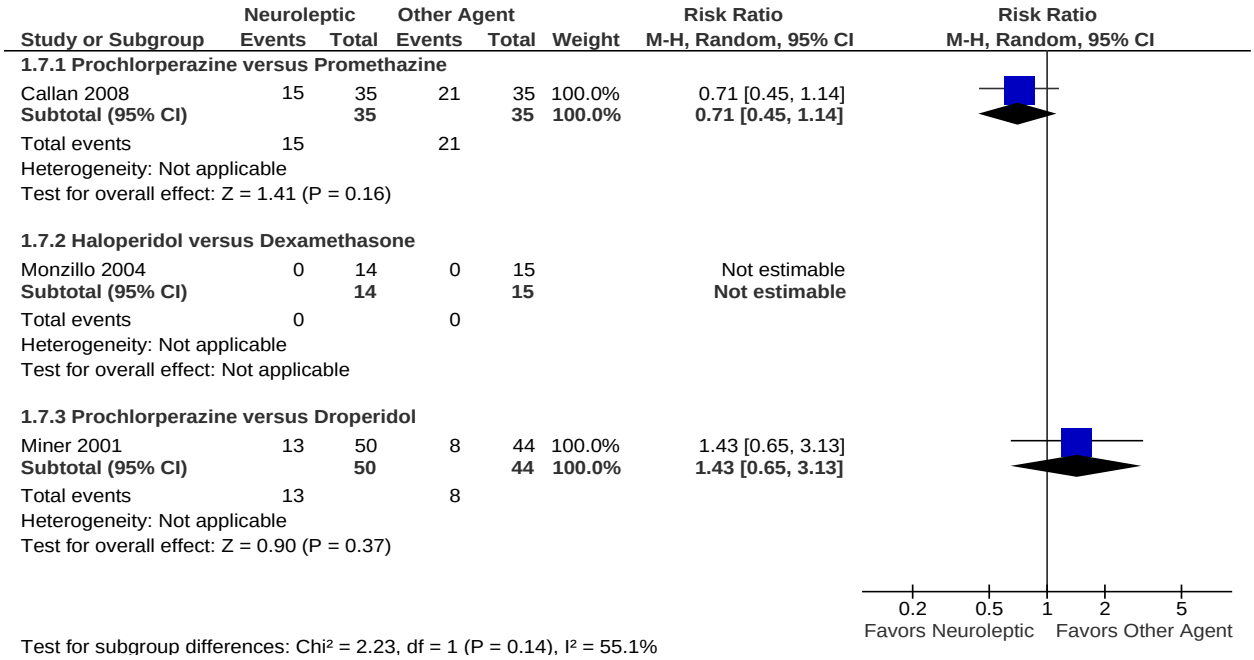
Sedation. Three studies assessed the effectiveness of neuroleptics versus other agents in the reduction of migraine-related sedation (Figure 16).[29,63,67] One study significantly favored octerotide over prochlorperazine (MD = 22.4; 95% CI: 3.23, 41.57).[67] In another study,[29] those who received prochlorperazine experienced a significant reduction in sedation compared with those who received prochlorperazine plus diphenhydramine (MD = -21.0; 95% CI: -30.85, -11.15).

Figure 16. Sedation in trials comparing neuroleptics and active agents



Headache recurrence. There were three studies evaluating headache recurrence 24 hours after discharge (Figure 17).[69,82,111] In the study comparing haloperidol with dexamethasone, no patients in either group reported a recurrent headache.[111] There were no statistically significant differences between groups for proclorperazine versus promethazine,[69] or prochlorperazine versus droperidol.[82]

Figure 17. Headache recurrence in trials comparing neuroleptics and active agents

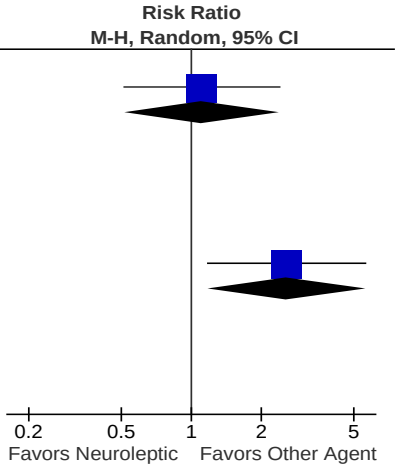


Akathisia. Two studies reported on the development of akathisia in the ED (Figure 18).[29,69] In both studies, more people in the prochlorperazine groups developed akathisia; however, the

results were only significant in one study where the other active agent was prochlorperazine plus diphenhydramine (RR = 2.57; 95% CI: 1.18, 5.61).[29] Diphenhydramine is an antihistamine agent used to prevent akathisia, and is used in combination with the neuroleptics and metoclopramide.

Figure 18. Akathisia in trials comparing neuroleptics and active agents

Study or Subgroup	Neuroleptic Events	Neuroleptic Total	Other Agent Events	Other Agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.8.1 Prochlorperazine versus Promethazine						
Callan 2008	10	35	9	35	100.0%	1.11 [0.51, 2.40]
Subtotal (95% CI)		**35**		**35**	**100.0%**	**1.11 [0.51, 2.40]**
Total events	10		9			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.27 (P = 0.79)						
1.8.2 Prochlorperazin versus Prochlorperazine + Diphenhydramine						
Vinson 2001	18	50	7	50	100.0%	2.57 [1.18, 5.61]
Subtotal (95% CI)		**50**		**50**	**100.0%**	**2.57 [1.18, 5.61]**
Total events	18		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.37 (P = 0.02)						



Test for subgroup differences: Chi² = 2.25, df = 1 (P = 0.13), I² = 55.6%

Nausea and vomiting. One study reported no statistically significant difference between methotrimetprazine and meperidine plus dimenhydrinate for residual nausea and vomiting (RR = 0.80; 95% CI: 0.36, 1.80).[60] In another study, resolution of nausea while in the ED was measured.[69] While a higher proportion of those who received prochlorperazine experienced nausea resolution compared with those receiving promethazine, the results were not statistically significant (RR = 1.34; 95% CI: 0.99, 1.83).

More than one dose required. One study reported no significant difference between those receiving chlorpromazine or meperidine and dimenhydrinate when comparing the need for antoher dose of medication (RR = 1.18; 95% CI: 0.80, 1.74).[61]

Patient satisfaction. One study measured patient satisfaction and found no difference between those who were administered prochlorperazine and those administered promethazine (RR = 1.00; 95% CI: 0.65, 1.54).[69]

Other outcomes. In one study, patients were contacted at home 1 day after discharge to determine rates of home drowsiness and agitation.[69] There was no significant difference in agitation between those who received prochlorperazine and those who received promethazine. When home drowsiness was reported, those in the prochlorperazine group experienced significantly less drowsiness (RR = 0.56; 95% CI: 0.35, 0.88).

Table 8. Strength of evidence for neuroleptics versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Neuroleptics vs. active agents	Change in pain–VAS (14; 1,127)	Moderate	Consistent	Direct	Not pooled	Moderate
	Headache recurrence (3; 193)	Moderate	Inconsistent	Direct	Not pooled	Low

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 9. Patient and study characteristics of trials comparing neuroleptics versus placebo or other active agents

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Neuroleptics versus placebo					
Bigal, 2002, Brazil, RCT [102]	60 min, (24 hr)	G1: CPZ, n=68, 0.1mg/kg IV P: Placebo, n=60, 10ml NR	G1: 34.7 (10.9), 50 (73.5), NR P: 27.7 (9.2), 41 (68.3), NR	G1: NR, NR P: NR, NR	1: pain intensity (10-pt verbal analogical scale and traditional 4-pt scale) 2: pain free, therapeutic gain, recurrence of pain, use of rescue medication, assessment of aura, associated symptoms (nausea, photophobia, phonophobia)
Coppola, 1992, U.S., RCT [87]	30 min, (48hr)	G1: MET, n=24, 10mg IV G2: PCZ, n=22, 10mg IV P: Placebo, n=24, NR IV	G1: NR, NR, NR G2: NR, NR, NR P: NR, NR, NR	G1: nonhatched VAS: 8.1, NR G2: nonhatched VAS:8.7, NR P: nonhatched VAS: 7.6, NR	1: median pain scores (nonhatched VAS) 2: median nausea scores, median sedation scores
Drotts, 1999, U.S., NRCT [85]	60 min, (48 hr)	G1: PCZ, n=100, 10 mg IV G2: Placebo or antibiotics, n=40, NR IV	G: 29.6 (10), 71 (71.0), NR G2: 31 (11), 16 (40.0), NR	G1: NR, NR G2: NR, NR	1: incidence of akathisia (Akathisia scale)
Honkaniemi, 2006, Finland, RCT [75]	1-3 hr, (1 mo)	G1: Haloperidol, n=20, 5 mg IV P: Placebo, n=NA, 500 ml IV	Total: 36, 41 (87.2), NR	G1: VAS: 7.7, 75 hr (total) P: VAS: 7.2, NA	1: pain (VAS) 2: relief from pain, side effects
Jones, 1989, U.S., RCT [62]	60min, (48hr)	G1: PCZ, n=42, 10mg IV P: Placebo, n=40, 2 ml IV	G1: 31.7(1.2), 28 (66.7), NR P: 32.4(0.9), 27 (67.5), NR	G1: NR, 9.7 (1.9)hr P: NR, 8.3 (2.1)hr	1: pain relief at 60 min (subjects asked to rate whether drug gave complete, partial, or no relief) 2: tx failures
Jones, 1996, U.S., RCT [86]	60 min (48 hr)	G1: PCZ, n=28, 10 mg IM	Total: 32.1 (2.1), 63 (73.3), NR	G1: VAS: 8.1 (range 6-10), NR	1: median pain score (VAS)

		G2: MET, n=29, 10 mg IM P: Placebo, n=29, 2 ml IM		G2: VAS: 8.5 (range 7-10), NR P: VAS: 8.0 (range 6-10), NR	2: nausea and vomiting
McEwen, 1987, Canada, RCT [92]	60min, (24hr)	G1: CPZ, n=19, 50mg IM P: Placebo, n=17, 2 ml IM	G1: 30, 18 (94.7), NR P: 36, 15 (88.2), NR	G1: NR, 27hr P: NR, 49hr	1: response to tx (no improvementj some improvement, but not enough to perform everyday activities; enough improvement to perform everyday activities and complete relief 2: successful tx response, some tx response, measures of dissatisfaction
Neuroleptics versus active agents					
Bell, 1990, Canada, RCT [91]	60 min (24hr)	G1: CPZ, n=24, 12.5mg IV G2: DHE, n=26, 1mg IV G3: LID, n=26, 50mg IV	Total: NR, 60 (79), NR	G1: Median intensity score (10-pt scale): 8.5; NR G2: Median intensity score (10-pt scale): 7.5; NR G3: Median intensity score (10-pt scale): 8.0; NR	1: headache response (10-pt scale, with 10 denoting the worst headache)
Blanda, 2001, U.S., RCT [83]	30 min, (NR)	G1: PCZ + LID, n=27, 10 mg PCZ + 2 ml of 4% LID IV and Intranasal G2: PCZ + Placebo, n=22, 10 mg PCZ + 2 ml saline IV and intranasal	G1: NR, 19 (86.4), NR G2: NR, 23 (85.2), NR	G1: VAS: 8.4, <4 hr: 5(18.5%); 4 to <12 hr: 8 (29.6%); 12 to 23 hr: 9 (33%) G2: VAS: 8.6, <4 hr: 2(9%); 4 to <12 hr: 10 (45.4%); 12 to 23 hr: 4 (18.1%)	1: pain reduction (VAS) 2: rescue medication, adverse reactions, dystonia, willingness to use IV delivery at home, return visits
Callan, 2007, U.S., RCT [69]	60 min, (NA)	G1: PMZ, n=35, 25 mg IV G2: PCZ, n=35, 10 mg IV	G1: 29.5, 30 (85.7), 15 (42.9) G2: 28.3, 27 (77.1), 19 (54.3)	G1: VAS: 70.7 mm, NR G2: VAS: 75.2 mm, NR	1: pain reduction (VAS) 2: headache within 5 d, akathisia in ED, rescue medication in ED, patient satisfaction, home drowsiness, home agitation, nausea resolution

Ginder, 2000, U.S., RCT [84]	30 min, (NA)	G1: $MgSO_4$, n=16, 2g IV G2: PCZ, n=20, 10 mg IV	G1: NR, 9 (56.3), NR G2: NR, 16 (80.0), NR	G1: VAS: 8.11 (1.98), NR G2: VAS: 8.25 (1.08), NR	1: Mean pain reduction (VAS)
Hill, 2008, U.S., RCT [68]	60 min, (NA)	G1: Olanzapine, n=50, 10 mg IM G2: DRO, n=50, 5 mg IM	G1: 32.5 (10.8), 35 (77.8), NR G2: 34.6 (9.3), 31 (73.8), NR	G1: VAS: 84.2 mm, 3 d (IQR: 1-4) G2: VAS: 83.9 mm, 3 d (IQR: 1-5)	1: pain (VAS) 2: nausea; median AMS score; median BAS awareness, distress
Kostic, 2010, U.S., RCT [58]	80 min (for 51 subjects), (NA)	G1: PCZ with DPH, n=32, 10 mg PCZ, 12.5 mg DPH IV G2: SUM, n=34, 6 mg SC	G1: 31 (10), 19 (61.3), NR G2: 28 (6), 23 (65.7), NR	G1: VAS: 76 mm (10), 2.7 (3.3) d G2: VAS: 71 mm (22), 1.7 (2.2) d	1: mean change in pain intensity for 80 min after tx (VAS) 2: mean degree of nausea and sedation
Lane, 1989, Canada, RCT [61]	105min, (60 min)	G1: CPZ, n=24, 0.04ml (0.1 mg/kg)/kg IV G2: MET + DMH, n=22, 0.1mg 0.4 mg/kg + 25mg IV	G1: 31.0 (range: 21-47), 21 (87.5), NR G2: 31.1 (range: 19-48), 18 (81.8), NR	G1: NR, 54.6 hr (range: 2-336) G2: NR, 41.8 hr (range: 2-216)	1: pain severity (VAS) 2: adverse side effects
Miller, 2009, U.S., RCT [67]	60 min (48 hr)	G1: Octreotide, n=24, 100 µg IV G2: PCZ, n=20, 10 mg IV	GI: 31.1 (11.1), 19 (79.2), NR G2: 27.5 (5.8), 14 (70.0), NR	GI: VAS: 75.4 (17.7), NR G2: VAS: 71.6 (15.3), NR	1: pain (VAS) 2: change in pain scale, change in nausea scale, change in sedation scale, occurrence of side effects (specifically restlessness consistent with akathisia)
Miner, 2001, U.S., RCT [82]	60 min, (24 hr)	G1: IV (33/82), IM (49/82); DRO, n=82, 5 mg (IM) or 2.5 mg (IV) G2: IV (29/86), IM (57/86); PCZ, n=86, 10 mg (IM) or 10 mg (IV)	G1: 31.7 (8.23), 42 (51.2), NR G2: 33.9 (12.1), 45 (52.3), NR	G1: VAS: 79.8 mm (95% CI: 75.7, 83.9), NR G2: VAS: 74.3 mm (95% CI: 69.6, 78.9), NR	1: pain (VAS) 2: side effects, rebound headaches, side effects beginning after discharge from the ED, seeking care elsewhere
Monzillo, 2004, Brazil, RCT [111]	120 min, (120 min)	G1: Haloperidol, n=14. 5 mg IV	Total: 31.5 (NR), 25 (86.2), NR	G1: NR, NR G2: NR, NR	1: pain intensity 2: pain recurrence, adverse effects

(Portugese)		G2: DEX, n=15, 4 mg IV			
Richman, 2002, U.S., RCT [80]	30 min, (NA)	G1: DRO, n=15, 2.5 mg IM G2: MEP, n=14, 1.5 mg/kg IM	G1: 30.7 (8.9), 11 (73.3), NR G2: 32.7 (9.9), 10 (71.4), NR	G1: VAS: 88 mm, 24.7 hr (28.3) G2: VAS: 76 mm, 18.3 hr (25.8)	1: pain (VAS) 2: drug preference (Likert scale)
Seim, 1998, U.S., RCT [65]	60 min (NA)	G1: PCZ , n=29, 10 mg IV G2: KET, n=35, 30 mg IV	G1: 34 (15), 27 (93.1), NR G2: 31 (9), 32 (91.4), NR	G1: VAS: 8.3 cm (2.1), NR G2: VAS: 8.4 cm (1.7), NR	1: pain score (VAS)
Shrestha, 1996, U.S., RCT [49]	120 min, (48 hr)	G1: KET, n=15, 60 mg IM G2: CPZ, n=15, 25 mg IV	G1: 30.8 (1.9), 11 (73.3), NR G2: 30.5 (1.45), 13 (86.7), NR	G1: Moderate to severe: 15 (100%), 4-72 hr duration: 15 (100%) G2: Moderate to severe: 15 (100%), 4-72 hr duration: 15 (100%)	1: mean pain scores (Wong-Baker Faces Rating Scale)
Stiell, 1991, Canada, RCT [60]	60 min (48hr)	G1: MTM, n=41, 37.5mg (25mg/ml) IM G2:MEP + DMH, n=41, 75mg + 50mg IM	G1:), 30.9 (7.3), 25 (67.6), NR G2: 32.5 (8.9), 31 (83.8), NR	G1: VAS: 7.97 (1.57), 23.9 (27.9) G2: VAS: 7.92 (13.50), 27.2 (32.6)	1: change in pain intensity (VAS) 2: proportion of patients with relief of 7.0 cm or more on the visual analog scale, residual nausea or vomiting
Tanen, 2003, U.S., RCT [63]	60 min, (NA)	G1: VAL, n=20, 500 mg IV G2: PCZ, n=20, 10 mg IV	G1: 31.0 (9.3), 11 (78.6), NR G2: 31.0 (10.0), 14 (70.0), NR	G1: VAS: 69.8 mm (18.3), NR G2: VAS: 76.1 mm (19.0), NR	1: pain (VAS)
Vinson, 2001, U.S., RCT [29]	60 min (NR)	G1: PCZ+ DMH, n=50, 10 mg + 50 mg IV G2: PCZ + Placebo, n=50, 10 mg IV	G1:31 (12.0), 32 (64.0) NR G2: 27 (9.3), 35 (70.0) NR	G1: NR, NR G2: NR, NR	1: akathisia 2: median sedation scores (VAS)
Weaver, 2003, U.S., RCT [64]	60 min, (24 hr)	G1: DRO, n=48, 2.5 mg IV G2: PCZ, n=48, 10 mg IV	G1: 30 (range: 18-68), 44 (91.7), White: 22 (45.8); Black: 26 (54.2); Other: 0 (0.0) G2: 34 (range: 19-64), 39 (81.3), White: 23 (47.9); Black: 23 (47.9: 2 (4.2));	G1: VAS median: 68 mm (range: 18-100), NR G2: VAS median: 79 mm (range: 21-100), NR	1: pain reduction at 30 min (VAS) 2: akathisia

			Other		

AMS = Altered Mental Status; BAS = Barnes Akathisia Scale; CPZ = chlorpromazine; DEX = dexamethasone; DHE = dihydroergotamine; DMH = dimenhydrinate; DPH = diphenhydramine; DRO = droperidol; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; IM = intramuscular; IV = intravenous; LID = lidocaine; MET = metoclopramide; mg = milligram(s); $MgSO_4$ = magnesium sulphate; min = minute(s); MTM = methotrimeprazine; N = number; NA = not applicable; NR = not reported; NRCT = non randomized controlled trial; P = placebo; PCZ = prochlorperazine; PMZ = promethazine; pt = point; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SUM = sumatriptan; tx = treatment; VAL = valproate; VAS = Visual Analogue Scale

Nonsteroidal Anti-inflammatory Drugs

Key Points

- More patients who received nonsteroidal anti-inflammatory drugs (NSAIDs) were pain free at 1–2 hours compared with those on placebo based on two RCTs (moderate strength of evidence).
- Fewer patients who received NSAIDs experienced headache recurrence compared with those receiving placebo based on one RCT (low strength of evidence).
- Results were mixed for patients who received NSAIDs compared with those receiving other active agents for improvement in pain intensity as measured by VAS (mm) based on five RCTs (low strength of evidence).
- Results were mixed for patients who received NSAIDs compared with those receiving other active agents for being pain free at 1–2 hours based on three RCTs (low strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who received NSAIDs compared with other active agents based on one RCT.

Results

The results for the NSAIDs studies are summarized below. Table 10 and Table 12 and provide the strength of evidence grades for all key outcomes.

NSAIDs versus Placebo

Description of Included Studies

Two RCTs assessed the effectiveness of NSAIDs compared with placebo in the treatment of acute migraine headaches.[95,96] The NSAIDs included lysine clonixinate[95] and diclofenac.[96] One study[95] was conducted in a headache clinic, and one[96] was conducted in a public health clinic. The mean age of participant groups was 32 years in one study.[95] The participants were predominantly female, and no study reported the race or ethnicity of study participants. Both studies reported pain relief or severity as the primary outcome at 60 to 120 minutes after administration. Post-ED followup timepoints ranged from 2 to 24 hours. The secondary outcomes included recurrence, use of rescue medication, and analgesic efficacy. See Table 13 for study and patient characteristics.

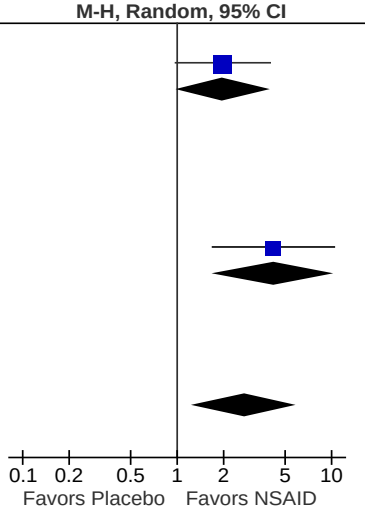
One study[96] had an unclear risk of bias, and the other[95] had a high risk of bias (Appendix D).

Effectiveness Results

Change in pain intensity (pain free). The change in pain intensity was measured as pain free at 1-2 hours in two studies[95,96] (Figure 19). The pooled results show that those who received NSAIDs experienced a decrease in pain intensity compared with those who received placebo (RR = 2.74; 95% CI: 1.26, 5.98; I^2= 47%).

Figure 19. Pain free at 1-2 hours in trials comparing NSAIDs and placebo

Study or Subgroup	NSAID Events	NSAID Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
48.1.2 Lysine Clonixinate versus Placebo						
Krymchantowski 2003	14	17	5	12	56.6%	1.98 [0.98, 4.00]
Subtotal (95% CI)		**17**		**12**	**56.6%**	**1.98 [0.98, 4.00]**
Total events	14		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.89 (P = 0.06)						
48.1.3 Diclofenac versus Placebo						
Bigal(2) 2002	21	60	5	60	43.4%	4.20 [1.70, 10.41]
Subtotal (95% CI)		**60**		**60**	**43.4%**	**4.20 [1.70, 10.41]**
Total events	21		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 3.10 (P = 0.002)						
Total (95% CI)		**77**		**72**	**100.0%**	**2.74 [1.26, 5.98]**
Total events	35		10			
Heterogeneity: Tau² = 0.15; Chi² = 1.88, df = 1 (P = 0.17); I² = 47%						
Test for overall effect: Z = 2.53 (P = 0.01)						
Test for subgroup differences: Chi² = 1.65, df = 1 (P = 0.20), I² = 39.5%						



Analgesic efficacy at 1 and 24 hours. One study measured analgesic efficacy at 1 hour and then again at 24 hours for diclofenac versus placebo.[96] They found that diclofenac was superior to placebo at 1 hour (RR = 3.11; 95% CI: 1.61, 6.02); however, no difference was found at 24 hours (RR = 1.14; 95% CI: 0.93, 1.39).

Headache recurrence. One study[96] reported headache recurrence, defined as return of pain within 24 hours after administration of the drug, and found that there was a statistically significant difference in favor of diclofenac (RR = 0.32; 95% CI: 0.17, 0.62).

Table 10. Strength of evidence for NSAIDs versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
NSAIDs vs. placebo	Pain free 1-2 hr (2; 149)	Moderate	Consistent	Direct	Precise	Moderate
	Headache recurrence (1; 120)	Moderate	Unknown	Direct	Precise	Insufficient

N = number; NSAID = nonsteroidal anti-inflammatory drug; ROB = risk of bias; VAS = Visual Analogue Scale

NSAIDs versus Active Agents

Description of Included Studies

Nine RCTs[50,51,76,79,89,97,108] assessed the effectiveness of NSAIDs versus other active agents. Three studies[50,89,97] specifically compared ketorolac to meperidine, of which two[50,89] were in combination with other agents. The NSAIDs included diclofenac[76,108] and lysine acetylsalicylic acid.[51] Other comparators included sumatriptan,[79] paracetamol,[108] ergotamine,[51] and tramadol.[76] Two studies have been described in another section of the report (neuroleptics) and compared NSAIDs with prochlorperazine[65] and chlorpromazine hydrochloride.[49]

All interventions were delivered in the ED, and assessments occurred between 60 and 180 minutes following administration. Followup occurred from 2 to 48 hours after patient discharge. For all trials, the number of participants who were randomized ranged from 29 to 112 (median = 47; IQR = 37, 68). The mean ages of intervention groups ranged from 18 to 56 years. All of the studies had a pain related primary outcome. The secondary outcomes varied and included use of rescue medication, adverse effects, and assessment of clinical disability. See Table 13 for study and patient characteristics. Table 9 reports study and patient characteristics for the studies described previously.[49,65]

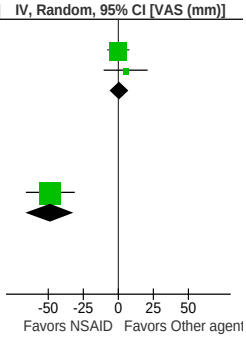
Two studies[49,76] had a low risk of bias, while the remaining seven studies had an unclear risk of bias (Appendix D).

Effectiveness Results

Pain intensity (VAS). Five studies[49,50,65,79,89] reported pain intensity using the VAS (mm) (Figure 20, Table 11). Table 11 describes the two studies that were analyzed in the neuroleptics section. All studies compared ketorolac to an active agent. One study[79] showed a significant difference in favor of NSAIDs when comparing ketorolac with nasal sumatriptan (MD = -48.53; 95% CI: -65.54, -31.51). One study showed a signficant difference in favor of prochlorperazine (MD = -19.00 (95% CI: -34.97, -3.03).[65] There was no difference when comparing ketorolac with meperidine plus hydroxyzine, ketorolac with meperidine plus promethazine (Figure 20), or ketorolac tropethamine with chlorpromazine hydrochloride (Table 11).

Figure 20. Pain intensity (VAS) in trials comparing NSAIDs and other active agents

Study or Subgroup	NSAID Mean [VAS (mm)]	NSAID SD [VAS (mm)]	NSAID Total	Other agent Mean [VAS (mm)]	Other agent SD [VAS (mm)]	Other agent Total	Weight	Mean Difference IV, Random, 95% CI [VAS (mm)]
1.11.1 Ketorolac versus Meperidine + Hydroxyzine or Promethazine								
Davis 1995	21.5	12.4	22	21.5	12.4	20	80.6%	0.00 [-7.51, 7.51]
Duarte 1992	-43.9	25.6	25	-49.1	29.4	25	19.4%	5.20 [-10.08, 20.48]
Subtotal (95% CI)			**47**			**45**	**100.0%**	**1.01 [-5.73, 7.75]**
Heterogeneity: Tau² = 0.00; Chi² = 0.36, df = 1 (P = 0.55); I² = 0%								
Test for overall effect: Z = 0.29 (P = 0.77)								
1.11.2 Ketorolac versus Sumatriptan								
Meredith 2003	-71.462	15.1216	13	-22.937	30.40852	16	100.0%	-48.53 [-65.54, -31.51]
Subtotal (95% CI)			**13**			**16**	**100.0%**	**-48.53 [-65.54, -31.51]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 5.59 (P < 0.00001)								

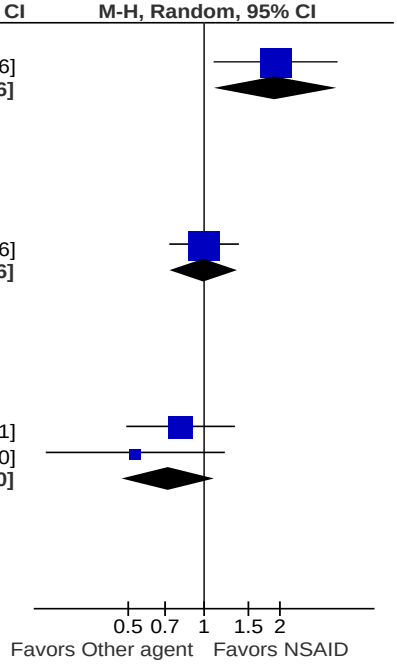


Test for subgroup differences: Chi² = 28.14, df = 1 (P < 0.00001), I² = 96.4%

Pain Response. Four studies reported a pain response after treatment (Figure 21).[50,51,76,97] One study [51] comparing lysine acetylsalicylic acid and ergotamine significantly favored NSAIDs (RR = 1.92; 95% CI: 1.10, 3.36). There was no significant difference between NSAIDs and other three active agents.[50,76,97] One study[76] also reported a pain response at 48 hours and found no difference between diclafenac and tramadol (RR = 0.92; 95% CI; 0.57, 1.49).

Figure 21. Pain response after treatment in trials comparing NSAIDs and other active agents

Study or Subgroup	NSAID Events	NSAID Total	Other agent Events	Other agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 Lysine acetylsalicylic acid versus Ergotamine						
Limmroth 1999	25	56	13	56	100.0%	1.92 [1.10, 3.36]
Subtotal (95% CI)		**56**		**56**	**100.0%**	**1.92 [1.10, 3.36]**
Total events	25		13			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.29 (P = 0.02)						
1.1.2 Diclofenac versus Tramadol						
Engindeniz 2005	16	20	16	20	100.0%	1.00 [0.73, 1.36]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.00 [0.73, 1.36]**
Total events	16		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
1.1.3 Ketorolac versus Meperidine (with or without Promethazine)						
Davis 1995	11	20	15	22	73.3%	0.81 [0.49, 1.31]
Larkin 1992	5	15	10	16	26.7%	0.53 [0.24, 1.20]
Subtotal (95% CI)		**35**		**38**	**100.0%**	**0.72 [0.48, 1.10]**
Total events	16		25			
Heterogeneity: Tau² = 0.00; Chi² = 0.76, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 1.52 (P = 0.13)						

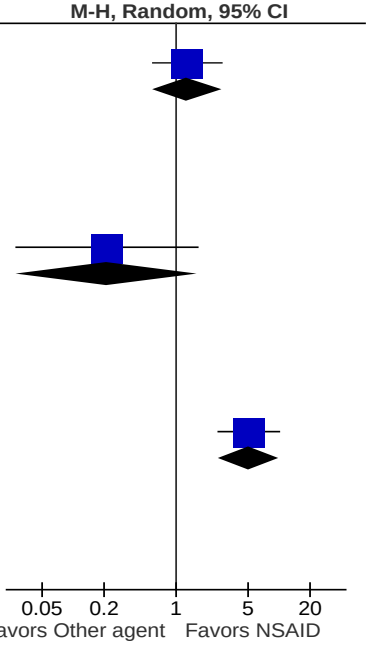


Test for subgroup differences: Chi² = 7.58, df = 2 (P = 0.02), I² = 73.6%

Pain free at 1-2 hours. Three studies reported being pain free at 1-2 hour (Figure 22).[76,97,108] One study[108] showed a significant difference in favor of NSAIDs when comparing diclofenac sodium versus paracetamol (RR = 5.08; 95% CI: 2.57, 10.03). There was no difference in the other two studies.[76,97] One study[76] reported being pain free at 48 hours and found no difference between diclofenac and tramadol (RR = 1.33; 95% CI: 0.57, 3.14).

Figure 22. Pain free at 1-2 hours in trials comparing NSAIDs and other active agents

Study or Subgroup	NSAID Events	NSAID Total	Other agent Events	Other agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Diclofenac versus Tramadol						
Engindeniz 2005	9	20	7	20	100.0%	1.29 [0.60, 2.77]
Subtotal (95% CI)		**20**		**20**	**100.0%**	**1.29 [0.60, 2.77]**
Total events	9		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.64 (P = 0.52)						
1.3.2 Ketorolac versus Meperidine						
Larkin 1992	1	15	5	16	100.0%	0.21 [0.03, 1.62]
Subtotal (95% CI)		**15**		**16**	**100.0%**	**0.21 [0.03, 1.62]**
Total events	1		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.49 (P = 0.14)						
1.3.3 Diclofenac Sodium versus Paracetamol						
Karachalios 1992	40	45	7	40	100.0%	5.08 [2.57, 10.03]
Subtotal (95% CI)		**45**		**40**	**100.0%**	**5.08 [2.57, 10.03]**
Total events	40		7			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.68 (P < 0.00001)						



Test for subgroup differences: Chi² = 12.66, df = 2 (P = 0.002), I² = 84.2%

Headache recurrence at 48 hours. One study[76] reported the recurrence of headache at 48 hours and found no difference between diclofenac and tramadol (RR = 1.50; 95% CI: 0.28, 8.04).

Additional analgesia. One study[89] reported the need for additional analgesia and found no difference between ketorolac and meperidine plus hydroxyzine (RR = 1.29; 95% CI: 0.57, 2.91).

Disability at 1 hour. One study[97] reported disability at 1 hour and found no difference between ketorolac and meperidine (RR = 0.64; 95% CI: 0.31, 1.32).

Table 11. Pain response after treatment in trials comparing NSAIDs and other active agents

Study, Year Study design (# patients)	Interventions	Risk of Bias	Outcomes	Data Source
NSAIDs vs. neuroleptics				
Seim, 1998 RCT (n = 64)	PCZ vs. ketorolac	Unclear	Pain intensity–VAS: MD = -19.00 (95% CI: -34.97, -3.03); favors neuroleptic agent	Figure 12
Shrestha, 1996 RCT (n = 30)	Tropethamine vs. chlorpromazine hydrochloride	Low	Pain intensity–VAS: MD = -5.30 (95% CI: -24.89, 14.29); favors neuroleptic agent	Figure 12

Table 12. Strength of evidence for NSAIDs versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
NSAIDs vs. active agents	Pain intensity–VAS (5; 215)	Moderate	Inconsistent	Direct	Not pooled	Low
	Pain free 1-2 hr (3; 156)	Moderate	Inconsistent	Direct	Not pooled	Low
	Pain response (4; 225)	Moderate	Inconsistent	Direct	Not pooled	Low
	Headache recurrence (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient

N = number; NSAID = nonsteroidal anti-inflammatory drug; ROB = risk of bias; VAS = Visual Analogue Scale

Table 13. Patient and study characteristics of trials comparing NSAIDs and placebo or active agents

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
NSAIDs versus placebo					
Bigal, 2002, Brazil, RCT[96]	60 min, (24 hr)	G1: Diclofenac, n=60, 75mg +10ml IM P: Placebo, n=60, 10ml IV	G1: NR, NR, NR P: NR, NR, NR	G1: NR, NR P: NR, NR	1: pain intensity (VAS) 2: analgesic efficacy, recurrence, rescue medication
Krymchantowski, 2003, Brazil, RCT[95]	120min, (2hr)	G1: Lysine clonixinate, n=17, 200mg IV P: Placebo, n=15, 25ml IV	Total: 32(2), 21 (72.4), NR	G1: NR, NR P: NR, NR	1: pain free (VAS) 2: rescue medication
NSAIDs versus active agents					
Davis, 1995, U.S., RCT[50]	60 min (NA)	G1: KET, n=20, 60mg IM G2: MEP + PMZ, n=22, 75mg MEP + 25mg PMZ IM	G1: 37.6, 17 (85.0), G2: 38.2, 17 (77.3),	G1: NR, NR G2: NR, NR	1: change in perceived headache pain (borg scale: patient subjective measurements)
Duarte, 1992, Canada, RCT[89]	60 min (NA)	G1: KET, n=25, 60mg IM G2: MEP + HDZ, n=25, 100mg + 50mg IM	G1: 34.9 (10.1), 20 (80.0), NR G2: 34.4 (12.3), 20 (80.0), NR	G1: VAS: 7.74 cm (1.84), 41.4 (38.1) G2: VAS: 8.28 cm (1.65), 16.5 (20.5)	1: pain-intensity scores (VAS) 2: required additional anesthesia at 30 and 60 min
Engindeniz, 2005, Turkey, RCT[76]	120 min, (48 hr)	G1: Diclofenac, n=24, 75 mg IM G2: Tramadol, n=23, 100 mg IM	G1: 37.9 (13.3), 14 (70.0), NR G2: 37.0 (11.06), 17 (85.0), NR	G1: NR, NR G2: NR, NR	1: pain response 2: 2-hr pain free, 48-hr pain and pain-free response, associated symptoms, rescue treatment, recurrence, adverse events
Karachalios, 1992, Greece, RCT[108]	180 min, (2-4 hr)	G1: Diclofenac sodium, n=46, 75mg IM G2: Paracetamol,	G1: 47.5, 21 (53.8), NR G2: 48.3, 26 (63.4), NR	G1: Severity of symptoms: slight (1), moderate (10), severe (35); NR G2: Severity of symptoms: slight (1), moderate (10), severe (30); NR	1: Partial or complete relief of pain

		n=40, 500 mg IM			
Larkin, 1992, U.S., RCT[97]	60 min, (24hr)	G1: KET, n=15, 30mg IM G2: MEP, n=16, 75mg IM	G1: 31.5 (4.4), 12 (80.0), NR G2: 33.8 (5.0), 12 (75.0), NR	G1: Grade 3 (most severe): 11 (73.3), Grade 2 (marked): 4 (26.7), Grade 1 (mild): 0 (0.0); NR G2: Grade 3 (most severe): 14 (87.5), Grade 2 (marked): 2 (12.5), Grade 1 (mild): 0 (0.0); NR	1: reduction in pain (4-pt verbal analogue scale) 2: assessment of clinical disability
Limmroth, 1999, Germany, RCT[51]	120min, (2hr)	G1: Lysine acetylsalicylic acid, n=56, 1000mg IV G2: Ergotamine, n=56, 0.5mg SC	Total: 41 (10.3), 48 (85.7) NR	G1: NR, NR G2: NR, NR	1: pain relief, (VAS) 2: improvement of nausea and vomiting
Meredith, 2003, U.S., RCT[79]	60 min, (NA)	G1: KET, n=13, 30 mg IV G2: SUM, n=16, 20 mg Nasal	G1: 33 (range: 18-54), total: 25 (86.2), NR G2: 34 (range: 19-56), total: 25 (86.2), NR	G1: VAS: 92.39 mm (10.94), NR G2: VAS: 84.63 mm (18.10), NR	1: pain score (VAS)

ED = emergency department; G1 = group 1; G2 = group 2; HDZ = hydroxyzine; hr = hour(s); IM = intramuscular; IV = intravenous; KET = ketorolac; MEP = meperidine; NR = not reported; NSAID = nonsteroidal anti-inflammatory drug; P = placebo; PMZ = promethazine; pt = point; RCT = randomized controlled trial; SD = standard deviation; SUM = sumatriptan; VAS = Visual Analogue Scale

Opioids

Key Points

- Patients who received opioids had greater improvement in pain intensity as measured by VAS (mm) compared with those on placebo based on three RCTs (moderate strength of evidence).
- Results were mixed for patients who received opioids compared with those who received active agents for improvement in pain intensity as measured by VAS (mm) based on 10 RCTs (low strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who were administered opioids compared with other active agent based on one RCT.

Results

The results for the opioid studies are summarized below. Table 14 provides the strength of evidence grades for all key outcomes.

Opioids versus Placebo

Description of Included Studies

Three RCTs assessed the effectiveness of opioids versus placebo in patients with acute migraine headache.[72,93,110] The opioids included pethidine,[110] nalbuphine,[93] nalbuphine plus hydroxyzine,[93] and tramadol.[72] All three studies were performed in the ED. The mean ages of patient groups ranged from 37 to 40 years. The participants were predominantly female, and no study reported the race of participants. All studies reported pain relief or severity as the primary outcome at a range from 45 to 60 minutes after administration of the drugs. Followup occurred in a range from 4 hours to 7 days after ED discharge. The secondary outcomes included headache recurrence and adverse effects. See Table 17 for details on study and patient characteristics.

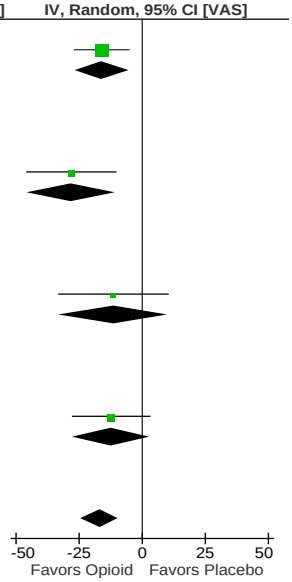
One study[93] had a low risk of bias, one[110] had an unclear risk of bias, and one[72] had a high risk of bias (Appendix D).

Effectiveness Results

Change in pain intensity (VAS). All three studies assessed pain intensity using the VAS (mm) (Figure 23). Pooled results demonstrated that opioids significantly decreased pain intensity compared with placebo (MD = -16.73; 95% CI: -24.12, -9.33; I^2 = 0%).

Figure 23. Pain intensity (VAS) in trials comparing opioids and placebo

Study or Subgroup	Opioid Mean [VAS]	Opioid SD [VAS]	Opioid Total	Placebo Mean [VAS]	Placebo SD [VAS]	Placebo Total	Weight	Mean Difference IV, Random, 95% CI [VAS]
2.1.1 Pethidine versus Placebo								
Cicek 2004	23	25	49	39	28.9	48	47.3%	-16.00 [-26.76, -5.24]
Subtotal (95% CI)			**49**			**48**	**47.3%**	**-16.00 [-26.76, -5.24]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.91 (P = 0.004)								
2.1.2 Nalbuphine versus Placebo								
Tek 1987	-47.9	32.9	23	-19.8	28.5	24	17.6%	-28.10 [-45.73, -10.47]
Subtotal (95% CI)			**23**			**24**	**17.6%**	**-28.10 [-45.73, -10.47]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.12 (P = 0.002)								
2.1.3 Tramadol versus Placebo								
Alemdar 2007	-32.7	28.21648	17	-21.3	35.69258	17	11.7%	-11.40 [-33.03, 10.23]
Subtotal (95% CI)			**17**			**17**	**11.7%**	**-11.40 [-33.03, 10.23]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.03 (P = 0.30)								
2.1.4 Hydroxyzine + Nalbuphine versus Placebo								
Tek 1987	-32.1	24.9	23	-19.8	28.5	24	23.4%	-12.30 [-27.58, 2.98]
Subtotal (95% CI)			**23**			**24**	**23.4%**	**-12.30 [-27.58, 2.98]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.58 (P = 0.11)								
Total (95% CI)			**112**			**113**	**100.0%**	**-16.73 [-24.12, -9.33]**
Heterogeneity: Tau² = 0.00; Chi² = 2.17, df = 3 (P = 0.54); I² = 0%								
Test for overall effect: Z = 4.43 (P < 0.00001)								
Test for subgroup differences: Chi² = 2.17, df = 3 (P = 0.54), I² = 0%								



Pain free response. One study[72] reported "pain free after treatment" and found no significant difference between tramadol and placebo (RR = 2.50; 95% CI: 0.56, 11.16).

Table 14. Strength of evidence for opioids versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Opioids vs. placebo	Pain intensity–VAS (3; 178)	Moderate	Consistent	Direct	Precise	Moderate

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Opioids versus Active Agents

Description of Included Studies

Twelve RCTs assessed the effectiveness of opioids versus other active agents. The opioids included meperidine,[50,89,97] pethidine,[110] tramadol,[76] nalbuphine,[93] meperidine plus dimenhydrinate,[60,109] nalbuphine plus hydroxyzine,[93] and butorphanol.[107] The other active agents included nalbuphine plus hydroxyzine,[93] hydroxyzine,[93] meperidine plus hydroxyzine,[107] and methotrimeprazine.[109] metoclopramide, methotrimeprazine, droperidol, chlorpromazine ketorolac, ketorolac plus promethazine, and DHE. Nine studies [48,50,60,61,76,80,89,97,110] have been described in other sections of the report (antiemetics, neuroleptics, NSAIDs, and DHE).

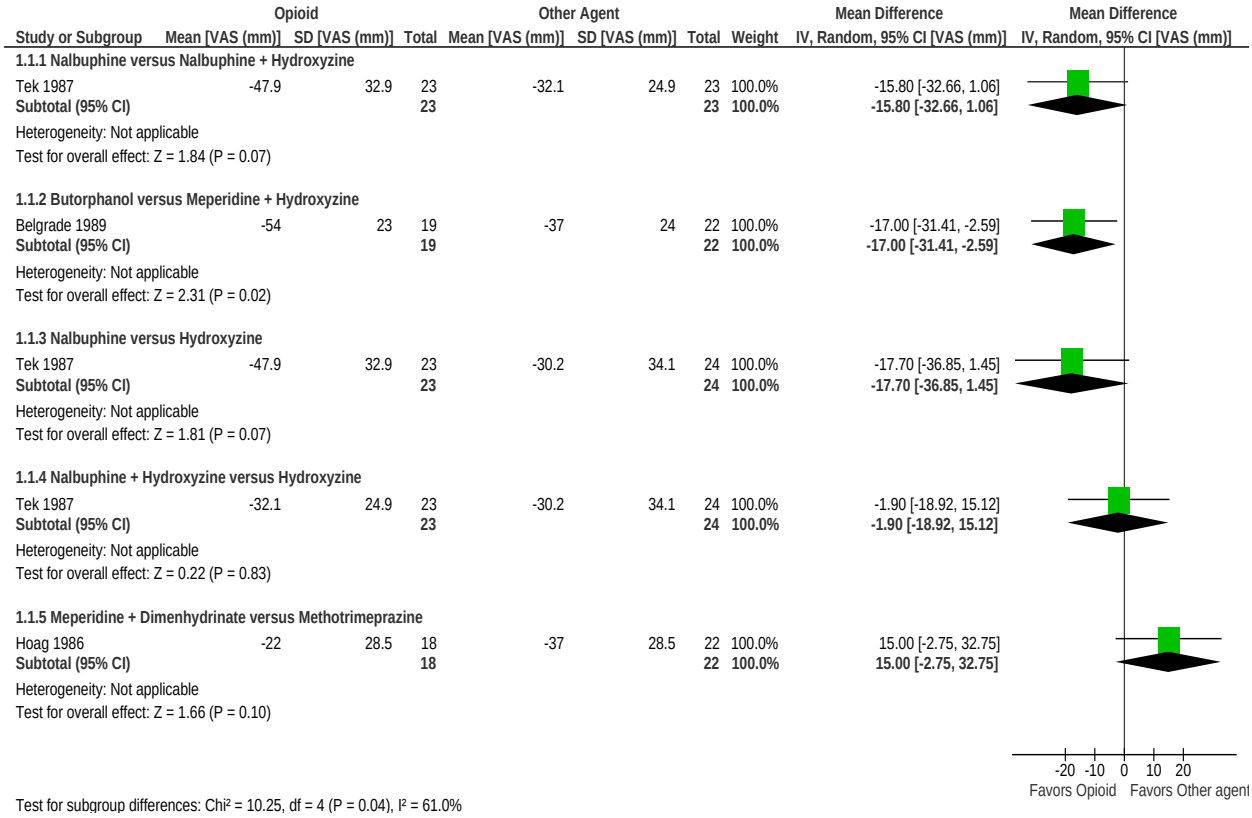
All interventions took place in the ED with outcomes assessed between 30 and 120 minutes after treatment. Post-ED followup ranged from 24 hours to 7 days. The mean ages of intervention groups ranged from 29 to 38 years. See the following tables for details on study and patient characteristics: Table 6 (antiemetics), Table 9 (neuroleptics), Table 13 (NSAIDs), Table 17 (opioids), and Table 19 (DHE).

Four studies had low risk of bias,[48,60,76,93] six studies[50,61,80,89,97,110] had unclear risk of bias, and two studies[107,109] had a high risk of bias (Appendix D).

Effectiveness Results

Change in pain intensity (VAS). The three studies[93,107,109] that have not been reported in other sections of the report used the VAS (MM) to measure pain intensity (Figure 24). One study[107] showed a significant result in favor of opioids when comparing butorphanol versus meperidine plus hydroxyzine (MD = -17.00; 95% CI: -31.41, -2.59). There was no statistically significant difference between opioids and other active agents in the other two studies. The studies that assessed pain intensity in previous sections of the report are described in Table 15.

Figure 24. Pain intensity (VAS) in trials comparing opioids and other active agents



Pain free response. Three studies[50,76,97] reported "pain free after treatment" and found no difference between opioids and other active agents. One trial[76] reported "pain free after 2 hours" and found a statistically significant difference in favor of opioids (RR = 1.29 (95% CI: 0.60, 2.77). The studies that assessed pain free status in previous sections of the report are described in Table 15.

Headache recurrence. One study[76] reported the recurrence of headache at 2 days following the intervention and found no difference between the interventions. The study that assessed headache recurrence previously in the report is described in Table 15.

Table 15. Opioids versus active agents in acute migraine

Study, Year Study design (# patients)	Interventions	Risk of Bias	Outcomes	Data Source
Antiemetics vs. opioids				
Cicek, 2004 RCT (n = 99)	Pethidine vs. metoclopramide	Unclear	Pain intensity–VAS: MD = -10.00 (95% CI: -19.21, -0.79); favors antiemetics	Figure 8
Neuroleptics vs. opioids				
Hoag, 1986 RCT (n = 40)	Meperidine + dimenhydrinate vs. methotrimeprazine	High	Pain intensity–VAS: MD = 15.00 (95% CI: -2.75, 32.75); favors neuroleptics	Figure 24
Lane, 1989 RCT (n=46)	Meperidine + dimenhydrinate vs. chlorpromazine	Unclear	Pain intensity–VAS: MD = -26.10 (95% CI: -40.10, -12.10); favors neuroleptics	Figure 12
Richman, 2002 RCT (n=28)	Meperidine vs. droperidol	Unclear	Pain intensity–VAS: MD = -10.00 (95% CI: -30.03, 10.03)	Figure 12
Stiell, 1991 RCT (n=74)	Meperidine + dimenhydrinate vs. methotrimeprazine	Low	Pain intensity–VAS: MD = 6.30 (95% CI: -4.77, 17.37)	Figure 12
Opioids vs. NSAIDs				
Davis, 1995 RCT (n=42)	Meperidine vs. ketorolac + promethazine	Unclear	Pain intensity–VAS: MD = 0.00 (95% CI: -7.51, 7.51) Pain free (post tx): RR = 0.81 (95% CI: 0.49, 1.31)	Figure 20
Duarte, 1992 RCT (n=50)	Meperidine vs. ketorolac	Unclear	Pain intensity–VAS: MD = 5.20 (95% CI: -10.08, 20.48)	Figure 20
Engindinez, 2005 RCT (n=40)	Tramadol vs. diclofenac	Low	Pain free (post tx): RR = 1.00 (95% CI: 0.73, 1.36); Pain free@2hr: RR = 1.29 (95% CI: 0.60, 2.77); favors opioids Headache recurrence@48hr: RR = 1.50 (95% CI: 0.28, 8.04)	Figure 21
Larkin, 1992 RCT (n=31)	Meperidine vs. ketorolac	Unclear	Pain free (post tx): RR = 0.53 (95% CI: 0.24, 1.20) Pain free@2hr: RR = 0.21 (95% CI: 0.03, 1.62)	Figure 21 Figure 22
Opioids vs. DHE				
Carleton, 1988 RCT (n=156)	Meperidine vs. DHE	Low	Pain intensity–VAS: MD = 2.20 (95% CI: -10.03, 14.43); favors DHE Functional improvement: RR = 2.27 (95% CI: 1.20, 4.29); favors opioids	Figure 25 Figure 26
Opioids vs. opioids				
Belgrade, 1989 RCT (n = 64)	Butorphanol vs. meperidine + hydroxyzine	High	Pain intensity–VAS: MD = -17.00 (95% CI: -31.41, -2.59); favors opioid	Figure 24
Tek, 1987 RCT (n = 74)	Nalbuphine + hydroxyzine vs. nalbuphine	Low	Pain intensity–VAS: MD = -15.80 (95% CI: -32.66, 1.06); favors opioid	Figure 24

CI = confidence interval; DHE = dihydroergotamine; hr = hour; RR = relative risk; RCT = randomized controlled trial; Tx = treatement; VAS = Visual Analog Scale

Table 16. Strength of evidence for opioids versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Opioids vs. active agents	Pain intensity–VAS (10; 673)	Moderate	Inconsistent	Direct	Not pooled	Low
Opioids vs. active agents	Headache recurrence	Low	Unknown	Direct	Imprecise	Insufficient

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 17. Patient and study characteristics of trials comparing opioids and placebo or active agents

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Opioids versus placebo					
Alemdar, 2007, Turkey, RCT[72]	60 min, (24 hr)	G1: Tramadol, n=17, 100 mg IV P: Placebo, n=17, 100 ml IV	G1: 42 (11.5), 13 (76.5), NR P: 37.1 (9), 15 (88.2), NR	G1: NR, NR P: NR, NR	1: pain response at 60 min (VAS) 2: pain-free response, adverse effects, headache recurrence
Cicek, 2004, Turkey, RCT[110]	45 min, (4 hr)	G1: MET, n=196 (Vascular headache); 140 (tension headache), IM Placebo + 10 mg IV MET G2: MET+PET, n=49, 10 mg IV MET+50 mg IM PET G3: PET, n=49, IV Placebo + 50 mg IM PET P: Placebo, n=48, NR IV and IM	Total: 38.8 (11.1) vascular headache; 42.1 (13.8) for tension headache; mean age of all subjects 40.2 (12.4), 7.1 (female to male ratio for vascular headache), 2.5 (in tension headache group),	G1: NR, NR G2: NR, NR P: NR, NR	1: pain intensity (VAS) 2: side effects
Tek, 1987, U.S., RCT[93]	60min, (7d)	G1: NAL, n=23, 10mg IM G2: NAL + HDZ, n=23, 10mg + 50mg IM G3: HDZ, n=24, 50mg IM P: Placebo, n=24, 2 ml IM	G1: NR, NR, NR G2: NR, NR, NR G3: NR, NR, NR P: NR, NR, NR	G1: NR, NR G2: NR, NR G3: NR, NR P: NR, NR	1: pain relief (4-pt scale)
Opioids versus active agents					
Belgrade, 1989, U.S., RCT[107]	30 min (72 hr)	G1: MEP+ HDZ, n=22, 75mg MEP+ 50mg HDZIM G2: BUT, n=19, 2mg IM G3: MET, n=23, 1mg DHE + 10mg MET IV	G1: 33 (11), 13 (59.1), NR G2: 29 (9), 11 (57.9), NR G3: 29(8), 13 (61.9), NR	G1: Initial pain score (1-100): 82(18), NR G2: Initial pain score (1-100): 84(11), NR	1: pain score improvement (scale of 1-100 where 100 is the worst possible pain) 2: blood pressure

				G3: Initial pain score (1-100): 83(19), NR	
Hoag, 1986, Canada, RCT[109]	Post tx, (24 hr)	G1: MEP+DMH, n=18, 75 mg + 50 mg IM G2: MTM, n=22, 25 mg IM	G1: NR, NR, NR G2: NR, NR, NR	G1: VAS: 8.1, NR G2: VAS: 8.4, NR	1: pain severity (VAS) 2: nausea
Tek, 1987, U.S., RCT[93]	60min, (7d)	G1: NAL, n=23, 10mg IM G2: NAL+HDZ, n=23, 10mg + 50mg IM G3: HDZ, n=24, 50mg IM P: Placebo, n=24, 2 ml IM	G1: NR, NR, NR G2: NR, NR, NR G3: NR, NR, NR P: NR, NR, NR	G1: NR, NR G2: NR, NR G3: NR, NR P: NR, NR	1: pain relief (4-pt scale)

BUT = butorphanol; DHE = dihydroergotamine; DMH = dimenhydrinate; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; HDZ = hydroxyzine; hr = hour(s); IM = intramuscular; IV = intravenous; MET = metoclopramide; MTM = methotrimeprazine; N = number; NAL = nalbuphine; NR = not reported; P = placebo; PET = pethidine; RCT = randomized controlled trial; SD = standard deviation; VAS = Visual Analogue Scale

Dihydroergotamine (DHE)

Key Points

- Results were mixed for patients who received DHE compared with those on other active agents for improvement in pain intensity as measured by VAS (mm) based on two RCTs (low strength of evidence).
- Results were mixed for pain relief at 2 hours for patients who were administered DHE compared with other active agents based on one RCT (low strength of evidence).
- Patients who received DHE had significantly poorer pain response than those who received NSAIDs based on one RCT (low strength of evidence).
- Fewer patients who received DHE experienced headache recurrence in 48 hours compared with sumatriptan based on one RCT (low strength of evidence).

Results

The results for the DHE studies are summarized below. Table 18 provides the strength of evidence grades for all key outcomes.

DHE versus Active Agents

Description of Included Studies

Five RCTs[48,51,56,88,91] with six comparisons assessed the effectiveness of DHE and other active agents. Active agents included meperidine,[48] diclofenac,[88] sumatriptan,[56] chlorpromazine,[91] lidocaine,[91] and lysine acetylsalicylic acid.[51] One study[51] was described in a previous section of this report (Table 13).

Three studies[48,51,91] were conducted in the ED, and two[56,88] were conducted in clinics managing acute headache patients. Assessments occurred immediately after treatment to 2 hours after treatment; followup assessments ranged from 2 to 24 hours following patient discharge. The number of participants who were randomized ranged from 34 to 310. The mean ages of intervention groups ranged from 32 to 42 years. All studies had a pain related primary outcome. The secondary outcomes varied and included adverse effects, functional impairment, recurrence, vital signs, and physician global rating. See Table 19 for details on study and patient characteristics.

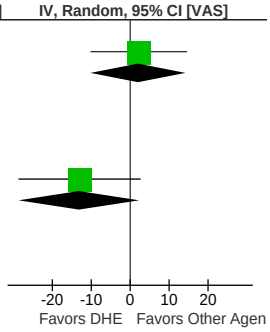
One study[48] had a low risk of bias, three studies had an unclear risk of bias,[51,56,88] and one study[91] had a high risk of bias (Appendix D).

Effectiveness Results

Change in pain intensity (VAS). Change in pain intensity was reported in two studies at 30 minutes[48] and 60 minutes.[48,88] There was no difference between DHE and meperidine at 30 minutes,[48] nor was there a difference at 60 minutes between DHE versus diclofenac or DHE versus meperidine (Figure 25).

Figure 25. Pain intensity (VAS) at 60 minutes in trials comparing DHE and other active agents

Study or Subgroup	DHE Mean [VAS]	DHE SD [VAS]	DHE Total	Other Agent Mean [VAS]	Other Agent SD [VAS]	Other Agent Total	Weight	Mean Difference IV, Random, 95% CI [VAS]
1.2.1 Dihydroergotamine versus Meperidine								
Carleton 1998	-53.4	41.4	78	-55.6	36.4	78	100.0%	2.20 [-10.03, 14.43]
Subtotal (95% CI)			**78**			**78**	**100.0%**	**2.20 [-10.03, 14.43]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.35 (P = 0.72)								
1.2.2 Dihydroergotamine versus Diclofenac								
Jovicic 1995	-70.5	21	17	-57.5	25	17	100.0%	-13.00 [-28.52, 2.52]
Subtotal (95% CI)			**17**			**17**	**100.0%**	**-13.00 [-28.52, 2.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.64 (P = 0.10)								



Test for subgroup differences: Chi² = 2.27, df = 1 (P = 0.13), I² = 56.0%

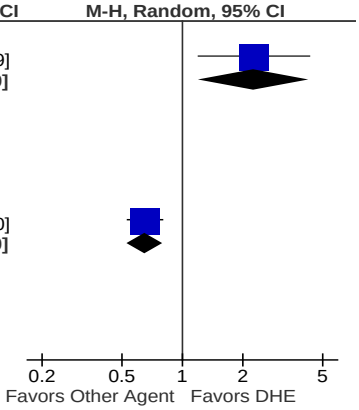
Pain relief. Pain relief was reported at 1, 2, 3, 4, and 24 hours in one study.[56] At both 1 and 2 hours, sumatriptan was more effective than DHE (RR = 0.73; 95% CI: 0.61, 0.86 and RR = 0.86; 95% CI: 0.76, 0.96, respectively). There were no differences at 3 and 4 hour assessments. At 24 hours, DHE was more effective than sumatriptan (RR = 1.17; 95% CI: 1.05, 1.30).

Pain Response. One study[51] comparing lysine acetylsalicylic acid and ergotamine significantly favored NSAIDs (RR = 1.92; 95% CI: 1.10, 3.36) (Figure 21).

Improvement of functional impairment. Two studies[48,56] reported improvement of functional impairment (Figure 26). Results were inconsistent across the studies.

Figure 26. Improved functional impairment in trials comparing DHE and other active agents

Study or Subgroup	DHE Events	DHE Total	Other Agent Events	Other Agent Total	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 Dihydroergotamine versus Meperidine						
Carleton 1998	25	78	11	78	100.0%	2.27 [1.20, 4.29]
Subtotal (95% CI)		**78**		**78**	**100.0%**	**2.27 [1.20, 4.29]**
Total events	25		11			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.53 (P = 0.01)						
1.3.2 Dihydroergotamine versus Sumatriptan						
Winner 1996	68	145	108	150	100.0%	0.65 [0.53, 0.80]
Subtotal (95% CI)		**145**		**150**	**100.0%**	**0.65 [0.53, 0.80]**
Total events	68		108			
Heterogeneity: Not applicable						
Test for overall effect: Z = 4.20 (P < 0.0001)						



Test for subgroup differences: Chi² = 13.50, df = 1 (P = 0.0002), I² = 92.6%

Headache recurrence. One study reported headache recurrence and found a significant difference in favor of DHE versus sumatriptan (RR = 0.39; 95% CI: 0.26, 0.59).[56]

Nausea and emesis. Two studies reported nausea, and one reported emesis. One study[56] showed a difference in favor of sumatriptan when compared with DHE for nausea (RR = 1.60; 95% CI: 1.10, 2.32). There was no difference when comparing DHE with

meperidine (RR = 0.94; 95% CI: 0.66, 1.35).[48] One study[56] compared DHE versus sumatriptan for emesis and found no difference (RR = 1.38; 95% CI: 0.49, 3.88).

Table 18. Strength of evidence for DHE versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
DHE vs. active agents	Pain intensity–VAS (2; 200)	Moderate	Inconsistent	Direct	Not Pooled	Low
	Pain relief at 2 hr (1;310)	Moderate	Inconsistent	Direct	Precise	Low
	Pain response (1; 112)	Moderate	Unknown	Direct	Precise	Low
	Headache recurrence (1; 156)	Moderate	Unknown	Direct	Precise	Low

DHE = dihydroergotamine; hr = hour(s); N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 19. Patient and study characteristics of trials comparing DHE and active agents

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Carleton, 1998, U.S., RCT[48]	60 min (24 hr)	G1: DHE, n=85, 1mg IM G2: MEP, n=85, 1.5mg/kg IM	G1: 32.52(8.82), 70 (82.3), NR G2: 32.36(8.78), 70 (82.3), NR	G1: Mean vascular score: 6.74(1.63), 33.75 hr (45.36) G2: Mean vascular score: 6.85 (1.82), 24.81 hr (25.71)	1: headache pain (VAS) 2: functional impairment, nausea, physician global assessment, vital signs, adverse events
Jovicic, 1995, Serbia, RCT[88] (Serbian)	After tx, (8 hr)	G1: DHE, n=17, 1mg IM G2: Diclofenac, n=17, 75mg IM	G1: 37.5 (10), 12 (70.6), NR G2: 38.4(8.4), 13 (76.5), NR	G1: Headache index: 30 (4), NR G2: Headache index: 34.2(4.5), NR	1: headache index
Bell, 1990, Canada, RCT[91]	60 min (24hr)	G1: CPZ, n=24, 12.5mg IV G2: DHE, n=26, 1mg IV G3: LID, n=26, 50mg IV	Total: NR, 60 (79), NR	G1: Median intensity score (10-pt scale): 8.5; NR G2: Median intensity score (10-pt scale): 7.5; NR G3: Median intensity score (10-pt scale): 8.0; NR	1: headache response (10-pt scale, with 10 denoting the worst headache)
Winner, 1996, U.S., RCT[56]	2 hr (24hr)	G1: DHE, n=152, 1mg SC G2: SUM, n=158, 6mg SC	G1: 40.5 (8.6), 133 (87.5), NR G2: 41.5, 139 (88.0), NR	G1: NR, NR G2: NR, NR	1: percentage of patients with relief (4-pt scale: none, mild, moderate, severe) 2: recurrence, functional ability, physicians global rating, nausea & emesis, safety

CPZ = chlorpromazine; DHE = dihydroergotamine; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; IM = intramuscular; IV = intravenous; LID =lidocaine; MEP = meperidine; NR = not reported; PET = pethidine; pt = point; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SUM = sumatriptan; tx = treatment; VAS = Visual Analogue Scale

Triptans

Key Points

- Patients who received sumatriptan had greater headache relief at 1 hour compared with those receiving placebo based on three RCTs (moderate strength of evidence).
- More patients who received sumatriptan were pain free at discharge compared with those receiving placebo based on four RCTs (moderate strength of evidence).
- Fewer patients who received sumatriptan experienced headache recurrence compared with those receiving placebo based on four RCTs (low strength of evidence).
- There was insufficient strength of evidence for headache relief at 1 hour for patients who received almotriptan compared with placebo based on one RCT.
- Results were mixed for patients who received triptans compared with those who received active agents for improvement in pain intensity as measured by VAS (mm) based on four RCTs (low strength of evidence).
- More participants who were administered sumatriptan experienced headache recurrence than those who were administered DHE based on one RCT (low strength of evidence).

Results

The results for the studies comparing triptans and placebo and active comparators are summarized below. Table 20 and Table 22 provide the strength of evidence grades for all key outcomes.

Triptans versus Placebo

Description of Included Studies

Six RCTs, all conducted in the ED, compared the effectiveness of triptans versus placebo in the treatment of acute migraine.[52-55,57,103] One publication reported the results of two separate trials;[53] in all metagraphs and analyses these individual trials are labeled as Mushet (1) and Mushet (2). Overall, 818 patients were treated with a triptan agent and 706 received placebo. All of the triptans were administered subcutaneously. Five studies evaluated sumatriptan (4-6 mg) and one evaluated almotriptan (2-10 mg).[57]

Most participants were female. The mean age ranged from 38 and 41 years. One study did not report any information on the age, sex, or race of participants.[55] Five studies evaluated participants in the ED for 120 minutes, while in one study patients were assessed at discharge.[103] Followup timepoints ranged from 12 hours to 5 days; patients were not contacted following discharge in one study.[55] All studies had primary outcomes that were related to pain including severity of headache and relief of pain. Secondary outcomes varied across studies and included nausea, vomiting, disability level, and mean duration of migraine attack. Study and patient characteristics are presented in Table 23.

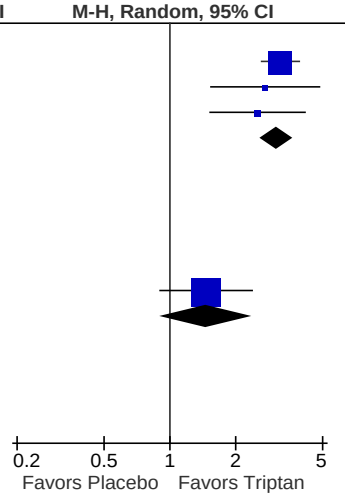
All six RCTs had an unclear risk of bias (Appendix D).[52-55,57,103]

Effectiveness Results

Headache relief at 60 minutes. Four trials assessed headache relief at 60 minutes (Figure 27).[53,55,57] In the three trials involving sumatriptan, the pooled results demonstrated that significantly more patients who received sumatriptan achieved headache relief than those who received placebo (RR = 3.06; 95% CI: 2.57, 3.65, I^2 = 0%). There was no statistically significant difference between patients who received almotriptan and those who received placebo.[57]

Figure 27. Headache relief at 60 minutes in trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.1.1 Sumatriptan						
Cady 1991	515	734	81	370	78.3%	3.20 [2.63, 3.91]
Mushet (1) 1996	28	40	10	39	9.4%	2.73 [1.54, 4.84]
Mushet (2) 1996	31	40	12	39	12.3%	2.52 [1.53, 4.15]
Subtotal (95% CI)		**814**		**448**	**100.0%**	**3.06 [2.57, 3.65]**
Total events	574		103			
Heterogeneity: Tau² = 0.00; Chi² = 0.97, df = 2 (P = 0.62); I² = 0%						
Test for overall effect: Z = 12.52 (P < 0.00001)						
4.1.2 Almotriptan						
Cabarrocas 2001	50	91	12	32	100.0%	1.47 [0.90, 2.38]
Subtotal (95% CI)		**91**		**32**	**100.0%**	**1.47 [0.90, 2.38]**
Total events	50		12			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.55 (P = 0.12)						

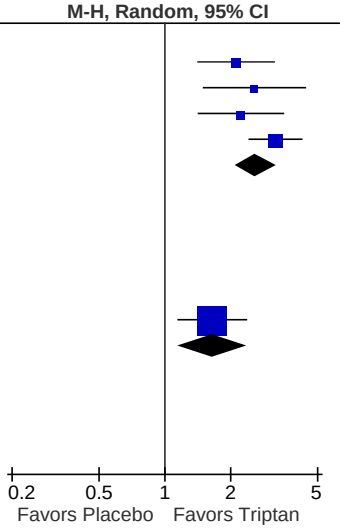


Test for subgroup differences: Chi² = 7.88, df = 1 (P = 0.005), I² = 87.3%

Headache relief at 120 minutes. There were five comparisons that evaluated headache relief at 120 minutes (Figure 28).[52,53,57,103] The difference between the triptan and placebo groups were statistically significant when participants were given sumatriptan (RR = 2.61; 95% CI: 2.09, 3.26; I^2 = 21%) or almotriptan (RR = 1.65; 95% CI: 1.15, 2.36).

Figure 28. Headache relief at 120 minutes in trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.2.1 Sumatriptan						
Akpunonu 1995	66	88	17	48	24.0%	2.12 [1.42, 3.16]
Mushet (1) 1996	29	40	11	39	14.8%	2.57 [1.50, 4.39]
Mushet (2) 1996	32	40	14	39	20.1%	2.23 [1.43, 3.48]
Wendt 2006	268	384	42	193	41.2%	3.21 [2.43, 4.22]
Subtotal (95% CI)		**552**		**319**	**100.0%**	**2.61 [2.09, 3.26]**
Total events	395		84			
Heterogeneity: Tau² = 0.01; Chi² = 3.80, df = 3 (P = 0.28); I² = 21%						
Test for overall effect: Z = 8.53 (P < 0.00001)						
4.2.2 Almotriptan						
Cabarrocas 2001	75	91	16	32	100.0%	1.65 [1.15, 2.36]
Subtotal (95% CI)		**91**		**32**	**100.0%**	**1.65 [1.15, 2.36]**
Total events	75		16			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.73 (P = 0.006)						



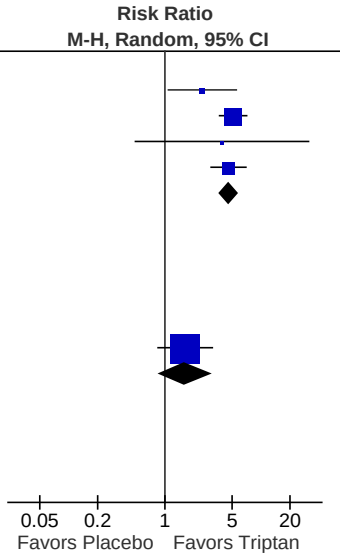
Test for subgroup differences: Chi² = 4.58, df = 1 (P = 0.03), I² = 78.2%

Pain relief. One study measured pain relief on the VAS (mm) at 30, 60, and 120 minutes.[52] The difference between the relief experienced by the sumatriptan and the placebo groups was statistically significant at all timepoints. Moreover, these difference increased at each timepoint: 30 minutes (MD = -15.45; 95% CI: -19.49, -11.41), 60 minutes (MD = -25.0; 95% CI: -29.32, -20.68), and 120 minutes (MD = -30.70; 95% CI: -35.02, -26.38). Another study measured pain relief at 30 minutes and found the results to be statistically significant in favor of triptans (MD = -18.5; 95% CI: -19.49, -11.41).[54]

Pain free. Five studies measured pain free status at discharge,[103] and at 30,[54] 60, and 120 minutes.[52,55,57] In the studies that compared sumatriptan versus placebo,[52,54,55,103] the pooled results showed a significant difference between groups (RR = 4.61; 95% CI: 3.62, 5.87, I^2 = 0%). In the study comparing almotriptan with placebo, more participants who were administered almotriptan achieved a pain free status as compared with those who were administered placebo, though the results were not significant (Figure 29).

Figure 29. Pain free status in trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.7.1 Sumatriptan						
Akpunonu 1995	27	88	6	48	8.9%	2.45 [1.09, 5.53]
Cady 1991	356	734	35	370	55.9%	5.13 [3.71, 7.09]
Thomson 1993	5	28	1	22	1.4%	3.93 [0.49, 31.23]
Wendt 2006	192	384	21	193	33.9%	4.60 [3.03, 6.97]
Subtotal (95% CI)		**1234**		**633**	**100.0%**	**4.61 [3.62, 5.87]**
Total events	580		63			
Heterogeneity: Tau² = 0.00; Chi² = 2.77, df = 3 (P = 0.43); I² = 0%						
Test for overall effect: Z = 12.37 (P < 0.00001)						
4.7.2 Almotriptan						
Cabarrocas 2001	37	91	8	32	100.0%	1.63 [0.85, 3.11]
Subtotal (95% CI)		**91**		**32**	**100.0%**	**1.63 [0.85, 3.11]**
Total events	37		8			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.47 (P = 0.14)						

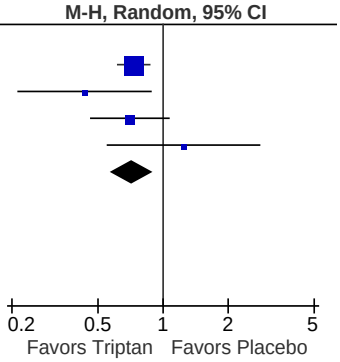


Test for subgroup differences: Chi² = 8.68, df = 1 (P = 0.003), I² = 88.5%

Headache recurrence. In four comparisons, patients were contacted within 24 hours of discharge to assess recurrence of migraine headache (Figure 30).[53,54,103] The pooled results demonstrated a significant difference in favor of sumatriptan (RR = 0.72; 95% CI: 0.57, 0.90, I^2 = 23%).

Figure 30. Headache recurrence at 24 hours in trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
4.6.1 Sumatriptan						
Akpunonu 1995	59	88	44	48	60.6%	0.73 [0.62, 0.87]
Mushet (1) 1996	8	40	18	39	9.4%	0.43 [0.21, 0.88]
Mushet (2) 1996	18	40	25	39	22.7%	0.70 [0.46, 1.06]
Thomson 1993	11	23	5	13	7.3%	1.24 [0.55, 2.79]
Subtotal (95% CI)		**191**		**139**	**100.0%**	**0.72 [0.57, 0.90]**
Total events	96		92			
Heterogeneity: Tau² = 0.01; Chi² = 3.90, df = 3 (P = 0.27); I² = 23%						
Test for overall effect: Z = 2.85 (P = 0.004)						



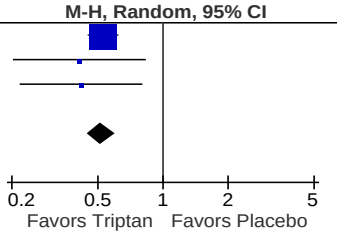
Test for subgroup differences: Not applicable

Nausea. There were three comparisons that assessed the effectiveness of sumatriptan in decreasing nausea at 60 minutes (Figure 31).[53,55] The pooled results demonstrated that sumatriptan significantly decreased nausea (RR = 0.52; 95% CI: 0.45, 0.60; I^2 = 0%).

Figure 31. Nausea at 60 minutes and trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cady 1991	198	734	189	370	90.3%	0.53 [0.45, 0.62]
Mushet (1) 1996	8	40	19	39	4.5%	0.41 [0.20, 0.83]
Mushet (2) 1996	9	40	21	39	5.2%	0.42 [0.22, 0.80]
Total (95% CI)		**814**		**448**	**100.0%**	**0.52 [0.45, 0.60]**
Total events	215		229			

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 8.79 (P < 0.00001)



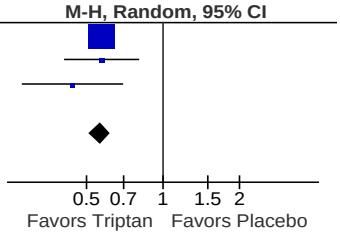
Vomiting. Two trials[53] assessed vomiting after the administration of sumatriptan versus placebo, and found no statistically significant difference between groups in either study (data not shown).

Photophobia. Three studies compared the effect of sumatriptan versus placebo on photophobia (Figure 32).[53,55] The pooled results show a significant difference between groups in favor of sumatriptan (RR = 0.57; 95% CI: 0.52, 0.62, I^2 = 0%).

Figure 32. Photophobia at 60 minutes and trials comparing triptans and placebo

Study or Subgroup	Triptan Events	Triptan Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Cady 1991	319	734	281	370	87.6%	0.57 [0.52, 0.63]
Mushet (1) 1996	20	40	34	39	8.0%	0.57 [0.41, 0.80]
Mushet (2) 1996	14	40	31	39	4.3%	0.44 [0.28, 0.69]
Total (95% CI)		**814**		**448**	**100.0%**	**0.57 [0.52, 0.62]**
Total events	353		346			

Heterogeneity: Tau² = 0.00; Chi² = 1.25, df = 2 (P = 0.53); I² = 0%
Test for overall effect: Z = 11.86 (P < 0.00001)



Phonophobia. Three studies compared sumatriptan and placebo and found a significant difference between groups for the occurrence of phonophobia in favor of sumatriptan (RR = 0.57; 95% CI: 0.42, 0.77, I^2 = 0%).[53,55]

Clinical disability. Two trials compared clinical disability rates between the sumatriptan and placebo groups at 120 minutes.[53] Significantly more patients in the placebo group were still experiencing clinical disability 1 hour after administration of the interventions (RR = 0.38; 95% CI: 0.25, 0.57, I^2 = 0%).

Other outcomes. One study assessed the difference in time to relief, time to discharge, and headache severity at discharge for participants receiving sumatriptan compared with placebo.[103] Each outcome was statistically significant in favor of sumatriptan (MD = -23.0; 95% CI: -36.33, -9.67; MD = -36.0; 95% CI: -53.58; -18.42; MD = -0.80; 95% CI: -1.40, -0.20, respectively).

Another study compared the duration of attack (hours), and time between dosing and attack (hours) for those who were administered almotriptan versus placebo.[57] For both outcomes, the differences between groups were not statistically significant.

Patient satisfaction with medication was assessed in two studies[53] in which participants were asked if they would "take the injectable form of medication again?" In both studies, significantly more patients who were given sumatriptan responded with "yes, definitely" and "probably" compared with those who were given placebo (RR = 1.53; 95% CI: 1.23, 1.89, I^2 = 0%).

Table 20. Strength of evidence for triptans versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Sumatriptan vs. placebo	Headache relief at 60 min (3; 1,262)	Moderate	Consistent	Direct	Precise	Moderate
	Pain free status (4; 1,867)	Moderate	Consistent	Direct	Precise	Moderate
	Headache relief at 120 min (4; 1,867)	Moderate	Consistent	Direct	Precise	Moderate
	Headache recurrence at 24 hr (4; 330)	Moderate	Inconsistent	Direct	Precise	Low
Almotriptan vs. placebo	Headache relief at 60 min (1; 123)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Pain free status (1; 123)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief at 120 min (1 RCT; 123)	Moderate	Unknown	Direct	Precise	Low

hr = hour(s); min = minute(s); N = number; RCT = randomized controlled trial; ROB = risk of bias

Triptans versus Active Agents

Description of Included Studies

Six studies compared sumatriptan with other active agents. The active agents included prochlorperazine and diphenhydramine,[58] metoclopramide,[77] chlorpromazine and metoclopramide,[32] trimethobenzamide and diphenhydramine,[74] DHE,[56] and ketorolac.[79] These studies are described in their sections of the report (e.g., antiemetics; neuroleptics; NSAIDs; DHE).

The interventions took place in the ED in all but one study.[56] The outcomes were assessed in the ED between 60 and 120 minutes; the post-ED followup, if applicable, occurred at 24 hours. The mean ages of the participant groups ranged from 28 to 41.5 years. Refer to the following tables for details on study and patient characteristics: Table 6 (antiemetics), Table 9 (neuroleptics), Table 13 (NSAIDs), Table 19 (DHE).

Two studies had low risk of bias,[58,74] three studies had unclear risk of bias,[56,77,79] and one study[32] had high risk of bias (Appendix D).

Effectiveness Results

Pain intensity (VAS). Four studies reported on this outcome (Table 21). Two studies comparing sumatriptan with antiemetics found no statistically significant difference. One study comparing a neuroleptic agent and sumatriptan reported a statistically significant difference in favor of the neuroleptics agent. One study comparing NSAIDs and sumatriptan reported a statistically significant difference in favor of the NSAIDs.

Pain relief. Pain relief was reported at 1, 2, 3, 4, and 24 hours in one study.[56] At both 1 and 2 hours, sumatriptan was more effective than DHE (RR = 0.73; 95% CI: 0.61, 0.86 and RR = 0.86; 95% CI: 0.76, 0.96, respectively). There were no differences at 3 and 4 hour assessments. At 24 hours, DHE was more effective than sumatriptan (RR = 1.17; 95% CI: 1.05, 1.30).

Headache recurrence. One study reported headache recurrence and found a significant difference in favor of DHE versus sumatriptan (RR = 0.39; 95% CI: 0.26, 0.59).[56]

Table 21. Triptans vs. other active agents

Study, Year Study design (# patients)	Interventions	Risk of Bias	Outcomes	Data Source
Antiemetics vs. triptans				
Friedman, 2005 RCT (n = 78)	MET vs SUM	Unclear	Pain intensity–VAS: MD = -9.00 (95% CI: -20.99, 2.99); favors antiemetic	Figure 8
Friedman, 2006 RCT (n = 40)	TMB + DPH vs. SUM	Low	Pain intensity–VAS: MD = 17.00 (95% CI: -0.08, 34.08); favors sumatriptan	Figure 8
Neuroleptics vs. triptans				
Kostic, 2010 RCT (n=66)	PCZ + DPH vs. SUM	Low	Pain intensity–VAS: MD = -23.00 (95% CI: -35.50, -10.50); favor neuroleptic	Figure 12
NSAIDs vs. triptans				
Meredith, 2003 RCT (n = 29)	KET vs. SUM	Unclear	Pain intensity–VAS: MD = -48.53 (95% CI: -65.54, -31.51); favors NSAIDs	Figure 20
DHE vs. triptans				
Winner, 1996 RCT (n = 310)	DHE vs. SUM	Unclear	Improved functional impairment: MD = 0.65 (95% CI: 0.53, 0.80); favors sumatriptan	Figure 26

CI = confidence interval; CPZ = chlorpromazine; DHE = dihydroergotamine; DPH = diphenhydramine; hr = hour; KET = ketorolac; MD = mean difference; MET = metoclopramide; PCZ = prochlorperazine; RCT = randomized controlled trial; SUM = sumatriptan; VAS = Visual Analog Scale; TMB = trimethobenzamide

Table 22. Strength of evidence for sumatriptan versus other active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Triptans vs. active agents	Pain intensity–VAS (4; 213)	Moderate	Inconsistent	Direct	Not pooled	Low
	Headache recurrence (1; 310)	Moderate	Unknown	Direct	Precise	Low

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 23. Patient and study characteristics of trials comparing triptans and placebo

Author, Year, Country Study design,	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Akpunonu, 1995, U.S., RCT [103]	discharge, (24 hr)	G1: SUM, n=88, 6mg SC P: Placebo, n=48, NR SC	G1: 39.8 (10); 78 (88.6); White: 78 (88.6), Black: 10 (11.4), Other: 0 (0.0) P: 39.8 (9.4); 41 (85.4); White: 44 (91.7), Black: 3 (6.3), Other: 1 (2.1)	G1: 4-pt pain scale: moderate 33 (37.5), severe 55 (62.5); 13hr (median) P: 4-pt pain scale: moderate 22 (45.8), severe 26 (54.2); 16 hr (median)	1: severity of headache (4-pt scale, 0-no pain, 1-mild, 2-moderate, 3- severe) 2: presence of nausea, vomiting, phonophobia or photophobia, clinical disability, time to "meaningful relief of headache"
Cabarrocas, 2001, Spain, RCT [57]	120 min, (3-5 d)	G1: ALMO, n=31, 2 mg SC G2: ALMO, n=29, 6 mg SC G3: ALMO, n=31, 10 mg SC P: Placebo, n=32, NR SC	G1: male and female: 39.5, 27 (87.1), NR G2: male: 39.6; female: 39.4, 22 (75.9), NR G3: male: 41.2; female: 40, 25 (80.6), NR P: male: 38.3; female: 41, 26 (81.3), NR	G1: NR, NR G2: NR, NR G3: NR, NR P: NR, NR	1: pain relief at 2 hr (self-assessed 4-pt scale) 2: pain relief at 1 hr, pain free at 2 hr, use of escape medication, mean time between dosing and end of attack, mean duration of attack
Cady, 1991, U.S., RCT [55]	120 min, (NA)	G1: SUM, n=187, 6 mg SC P: Placebo, n=370, 0.5 ml SC	G1: NR, NR, NR P: NR, NR, NR	G1: NR, NR P: NR, NR	1: headache severity (4-pt scale) 2: pain relief, clinical disability, nausea, vomiting, photophobia
Mushet, 1996, U.S., RCT [53]	120 min, (24 hr)	G1: SUM, n=40+39, 6 mg SC P: Placebo, n=40+39, NR SC	G1: 40.3, 36 (90.0) + 37 (94.9), NR P: 39, 33 (82.5) + 31 (79.5), NR	G1: NR, NR P: NR, NR	1: headache relief 2: nausea, vomiting, photophobia and phonophobia, clinical disability, meaningful relief of headache, would patient use the medication again to treat migraine, headache relief (reduction in score from 3 or 2 before tx or 1 or 0 at 60 min on 4-pt scale)
Thomson, 1993, New Zealand, RCT [54]	120 min, (24 hr)	G1: SUM, n=28, 4mg SC P: Placebo, n=23,	Total: 41, 43 (86.0), NR	G1: 4-pt pain scale:2.2; 7.8 hr (median) P: 4-pt pain scale: 2.2; 5.3 hr (median)	1: number of patients obtaining headache improvement from severe or moderate grade 3 or 2 to 1 or 0 within 30 min of receiving

		0.5ml SC			injection 2: alteration of associated symptoms (nausea, vomiting, photophobia), disability level, need for rescue medication, recurrence of headache, headache improvement (change in 4-pt pain scale)
Wendt, 2006, U.S., RCT [52]	120 min, (12-24 hr)	G1: SUM, n=384, 0.66ml SC (corresponds with to 4mg) P: Placebo, n=193, 0.66ml SC	G1: 38.3 (9.5), 331 (86.2), White: 366(95.3), Black: 10 (2.6), Other: 8 (2.1) P: 38.1(9.7), 170 (88.1), White: 175 (90.7), Black: 7 (3.6), Asian: 1 (0.5), Other: 10 (5.2)	G1: Severity of pain mild: 3 (0.80), moderate: 179 (46.6), severe: 202 (52.6); at least 72 hr P: Severity of pain mild: 2 (1.0), moderate: 99 (51.3), severe: 92 (47.7); at least 72 hr	1: headache severity (4-pt scale) 2: pain relief, presence or absence of nausea, vomiting or photophobia

ALMO = almotriptan; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; NA = not applicable; NR = not reported; P = placebo; RCT = randomized controlled trial; SC = subcutaneous; SD = standard deviation; SUM = sumatriptan; VAS = Visual Analogue Scale

Magnesium Sulphate

Key Points

- There was no difference in improvement in pain intensity as measured by the VAS (mm) for patients who received magnesium sulphate ($MgSO_4$) compared with those receiving placebo based on two RCTs (low strength of evidence).
- There was no difference in pain reduction for patients who received $MgSO_4$ compared with those receiving placebo based on two RCTs (low strength of evidence).
- There was insufficient strength of evidence for headache recurrence for patients who received $MgSO_4$ compared with placebo based on one RCT.
- $MgSO_4$ was less effective in improving pain intensity than other active agents based on two RCTs (moderate strength of evidence).

Results

The results for the three studies that assessed $MgSO_4$ are summarized below. Table 24 provides the strength of evidence grades for all key outcomes.

Magnesium Sulphate versus Placebo

Description of Included Studies

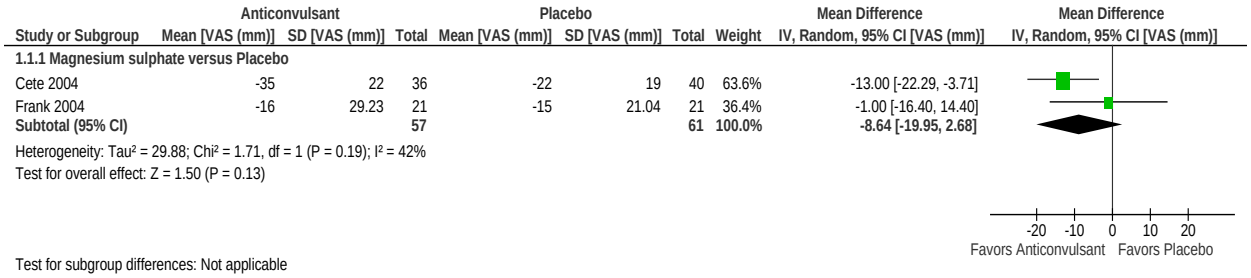
Three RCTs[66,78,94] assessed the effectiveness of $MgSO_4$ compared with placebo. One study[66] was conducted in a clinic managing acute headaches, and two[78,94] took place in the ED. The mean ages of participant groups ranged from 29 to 40 years. The participants were predominantly female. One study[94] reported that participants were predominantly white. All studies reported pain relief or severity as the primary outcome. Timepoints ranged from 20 to 30 minutes. Post-ED followup was 24 hours. The secondary outcomes included recurrence, use of rescue medication, and adverse effects. See Table 27 for details on the study and patient characteristics.

Two studies[78,94] had a low risk of bias, while one study[66] had an unclear risk of bias (Appendix D).

Effectiveness Results

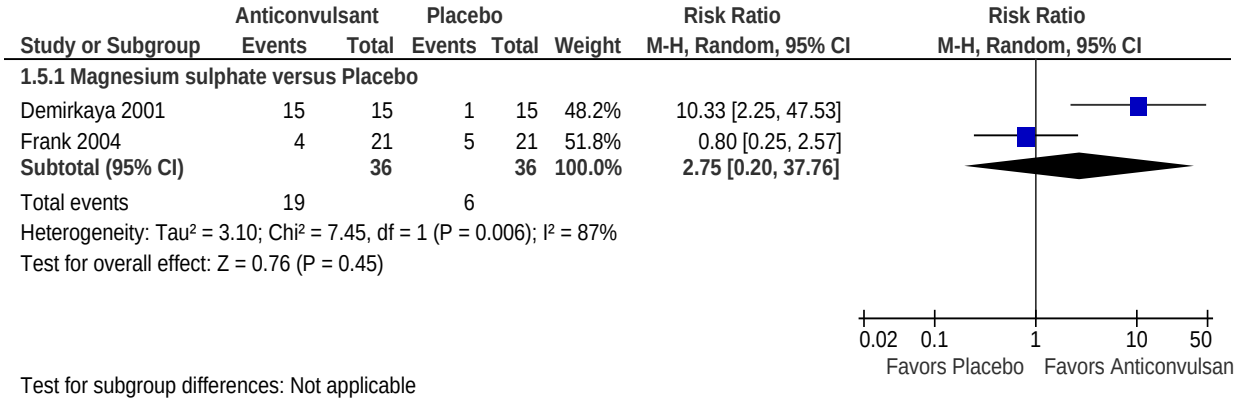
Change in pain intensity (VAS). Two studies reported pain intensity using the VAS (mm) (Figure 33).[78,94] No difference was observed in the pooled analysis (MD = -8.64; 95% CI: -19.95, 2.68; I^2 = 42%).

Figure 33. Pain intensity (VAS) in trials comparing $MgSO_4$ and placebo



Pain reduction. Two studies reported pain reduction.[66,94] There was no difference observed between $MgSO_4$ versus placebo (RR = 2.75; 95% CI: 0.20, 37.76; I^2 = 87%); however, the heterogeneity was high (Figure 34).

Figure 34. Pain reduction in trials comparing $MgSO_4$ and placebo



Headache recurrence. One study[78] reported headache recurrence and found no difference between $MgSO_4$and placebo (RR = 1.01; 95% CI: 0.66, 1.54).

Table 24. Strength of evidence for $MgSO_4$ versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
$MgSO_4$ vs. placebo	Pain intensity–VAS (2; 118)	Low	Inconsistent	Direct	Imprecise	Low
	Pain reduction (2; 72)	Moderate	Inconsistent	Direct	Imprecise	Low
	Headache recurrence (1; 76)	Low	Unknown	Direct	Imprecise	Insufficient

$MgSO_4$ = magnesium sulphate; N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Magnesium Sulphate versus Active Agents

Description of Included Studies

One study compared the effectiveness of $MgSO_4$ and prochlorperazine[84] and one study compared $MgSO_4$ and metoclopramide.[78] These studies have been described previously in other sections of the report (antiemetics; neuroleptics).

In both studies, the interventions took place in the ED and outcomes were measured in the ED at 30 minutes. One study[78] also assessed participants at 24 hours post intervention. One study[84] did not report the mean age of participants while the other study[78] reported a mean age of 40 years. See the following tables for details on study and patient characteristics: Table 6 (antiemetics), Table 9 (neuroleptics).

Both studies had a low risk of bias (Appendix D).

Effectiveness Results

Table 25 summarizes results for the studies that compared $MgSO_4$ and other active agents. Two studies reported pain intensity (VAS). In one study metoclopramide was more effective than $MgSO_4$ and the results were statistically significant. In the other study comparing neuroleptics and $MgSO_4$, the results were not statistically significant.

Table 25. Pain response in trials comparing $MgSO_4$ and other active agents

Study, Year Study Design (# patients)	Interventions	Risk of Bias	Outcomes	Data Source
Antiemetics vs. $MgSO_4$				
Cete, 2004 RCT (n = 113)	MET vs. $MgSO_4$	Low	Pain intensity–VAS: MD = -5.00 (95% CI: -15.80, 5.80); favors antiemetics	Figure 8
Neuroleptics vs. $MgSO_4$				
Ginder, 2000 RCT (n=36)	PCZ vs. $MgSO_4$	Low	Pain intensity–VAS: MD = -23.00 (95% CI: -44.67, -1.33); favors neuroleptics	Figure 12

CI = confidence interval; MD = mean difference; MET = metoclopramide; PCZ = prochlorperazine; RCT = randomized controlled trial; VAS = Visual Analog Scale

Table 26. Strength of evidence for $MgSO_4$ versus active agents

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
$MgSO_4$ vs. active agents	Pain intensity–VAS (2; 149)	Low	Consistent	Direct	Not pooled	Moderate

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 27. Patient and study characteristics of trials comparing $MgSO_4$ and placebo

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Cete, 2004, Turkey, RCT [78]	30min, (24 hr)	G1: $MgSO_4$, n=36, 2 g IV P: Placebo, n=40, 100 ml IV	G1: 40 (12), 27 (75.0), NR P: 40 (11), 35 (87.5), NR	G1: VAS: 70 mm (22), NR P: VAS: 69 mm (19), NR	1: pain intensity at 30 min (VAS) 2: adverse effects, rescue medication, recurrence at 24 hr
Frank, 2004, Canada, RCT [94]	30 min, (NA)	G1: $MgSO_4$, n= 21, NR IV P: Placebo, n=21, NR IV	G1: 36 (8), 15 (71.4), White: 18 (85.7) P: 29(8), 17 (81.0), White: 18 (85.7)	G1: VAS: 80 mm (13), NR P: VAS: 78 mm (16), NR	1: median difference in VAS pain score 2: changes in nausea, vomiting and photophobia, % patients achieving a 50% reduction in pain, % patients needing rescue medication
Demirkaya, 2001, Turkey, RCT [66]	.20 min, (24hr)	G1: $MgSO_4$,, n=15, 1g IV P: Placebo, n=15, 10 ml IV	G1: NR, NR, NR P: NR, NR, NR	G1: NR, NR P: NR, NR	1: pain intensity (categorized into four groups: 0 = no pain; 1 = mild pain, is not interfering with daily activities; 2 = moderate pain, is affecting daily activities but not hindering them; 3 = severe pain) 2: side effects

ED = emergency department; g = gram(s); G1 = group 1; hr = hour(s); IV = intravenous; $MgSO_4$ = magnesium sulphate; NR = not reported; P = placebo; RCT = randomized controlled trial; SD = standard deviation; VAS = Visual Analogue Scale

Antihistamines

Key Points

- There was insufficient strength of evidence for improvement in pain intensity as measured by VAS (mm) for patients who received hydroxyzine compared with placebo based on one RCT.

Antihistamine versus Placebo

Description of Included Studies

One RCT[93] compared the effectiveness of antihistamines and placebo in the treatment of acute migraine headache. The antihistamine was hydroxyzine. The study was conducted in the ED. The mean age of patients was not reported. This study reported pain relief as the primary outcome, measured at 60 minutes. Post-ED followup occurred at 7 days. There were no secondary outcomes reported (Table 29). The study had a low risk of bias (Appendix D).

Effectiveness Results

Pain relief (VAS). The authors found no difference in pain relief comparing hydroxyzine with placebo (MD = 10.40; 95% CI: -7.38, 28.18).[93]

Table 28. Strength of evidence for antihistamine versus placebo

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Antihistamine vs. placebo	Pain intensity–VAS (1; 48)	Low	Unknown	Direct	Imprecise	Insufficient

N = number; ROB = risk of bias; VAS = Visual Analogue Scale

Table 29. Patient and study characteristics of trials comparing antihistamine and placebo

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Tek, 1987, U.S., RCT[93]	60min, (7d)	G1: HDZ, n=24, 50mg IM P: Placebo, n=24, 2ml IM	G1: NR, NR, NR P: NR, NR, NR	G1: NR, NR P: NR, NR	1: pain relief (4-pt scale)

ED = emergency department; G1 = group 1; HDZ = hydroxyzine; IM = intramuscular; NR = not reported; P = placebo; pt = point; RCT = randomized controlled trial; SD = standard deviation

Active Combination Therapy versus Active Therapy

Key Points

- Eight RCTs compared seven different combination interventions with other active agents. There was insufficient evidence about the effectiveness of specific combination therapy for pain relief.
- A post hoc mixed treatment analysis found that combination therapy (metoclopramide plus DHE and prochlorperazine plus DHE) and neuroleptic agents were most effective in pain relief (low strength of evidence).

Description of Included Studies

Eight RCTs[32,81,98,100,104,105,107,110] assessed the effectiveness of two active interventions versus one or more active interventions. Table 31 summarizes study and patient characteristics. The studies were all performed in the ED. The mean ages ranged from 29 to 43 years. None of the trials used the same combination of drugs in their studies. Five trials[32,81,105,107,110] with six separate interventions reported a pain reduction as their primary outcome on the VAS (mm), which was measured between 30 and 120 minutes post-treatment. Two trials[100,104] reported headache relief after therapy as a dichotomous outcome measured at 30 minutes and 4 hours. Risk of bias was unclear for five trials,[81,98,104,105,110] and high for three[32,100,107] (Appendix D).

Effectiveness Results

Three interventions[98,107,110] reported a statistically significant result that favored metoclopramide plus DHE versus meperidine plus hydroxyzine, metoclopramide plus DHE versus ketorolac monotherapy, and metoclopramide plus pethidine versus pethidine monotherapy (Table 30). The strength of evidence was insufficient for all of the studies because there were single trials with small sample sizes.

Table 30. Summary of studies reporting active combination therapy versus active therapy for pain

Author, Year, Study Design	Intervention	Sample Size	Risk of Bias	Effect Estimate (95% CI)	Strength of Evidence
Belgrade, 1989, RCT[107]	MET+DHE vs. BUT	45	High	MD = -5.00 (-19.98, 9.98)	Insufficient
Belgrade, 1989, RCT[107]	MET+DHE vs. MEP+HDZ	45	High	**MD = -22.0 (-36.66, -7.34)*,** favors MET+DHE	Insufficient
Callaham,1986, RCT[105]	PCZ+DHE vs. PCZ	34	Unclear	MD = 5.00 (-18.96, 28.96)	Insufficient
Cicek, 2004, RCT [110]	MET+PET vs. MET	245	Unclear	MD = 0.00 (-8.47, 8.47)	Insufficient
Cicek, 2004, RCT[110]	MET+PET vs. PET	98	Unclear	**MD = -10.0 (-19.2, -0.79)***, favors MET+PET	Insufficient
Corbo, 2001, RCT[81]	MET+$MgSO_4$ vs MET	44	Unclear	MD = 16.00 (-1.58, 33.58)	Insufficient
Edwards, 2001, RCT[100]	MET+DHE vs. VAL	40	High	RR = 1.10 (0.61,1.99)	Insufficient
Kelly, 1997, RCT[32]	MET+CPZ vs MET+SUM	43	High	MD = 9.00 (-4.04, 22.04)	Insufficient
Klapper, 1991, RCT[98]	MET+DHE vs. KET	18	Unclear	**MD = -30.0 (-57.72, -2.28)*;** favors MET+DHE]	Insufficient
Klapper, 1989, RCT[104]	MET+DHE vs MET+DEX	20	Unclear	RR = 0.95 (0.61, 1.49)	Insufficient

* = significant result; BUT = butorphanol; CPZ = chlorpromazine; DEX = dexamethasone; DHE = dihydroergotamine; ED = emergency department; HDZ = hydroxyzine; KET = ketorolac; MD = mean difference; MEP = meperidine; MET =

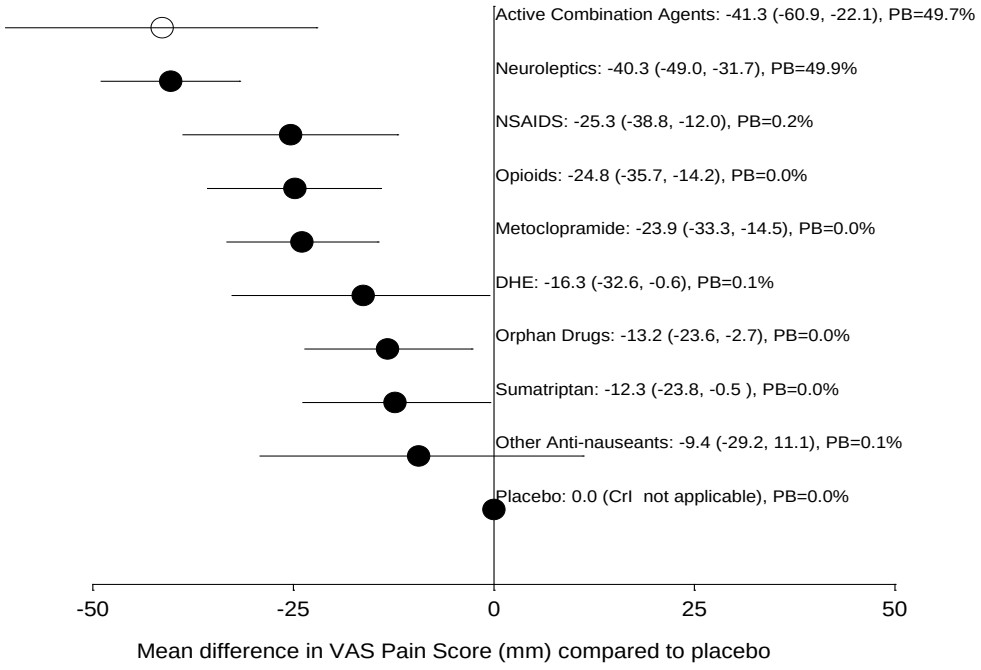
metoclopramide; $MgSO_4$ = magnesium sulphate; PET = pethidine; PCZ = prochlorperazine; RCT = randomized controlled trial;; RR = relative risk; SUM = sumatriptan; VAL = valproate

Mixed treatment analysis for pain relief (VAS)

We conducted a post hoc mixed treatment analysis of 36 studies that reported a pain score (VAS). In addition to neuroleptic agents, metoclopramide, NSAIDs, opioids, DHE, sumatriptan, and orphan drugs (i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide), we examined active combination agents. The combination agents were metoclopramide plus DHE[98,107] and prochlorperazine plus DHE.[105] The results showed that both combination therapy and neuroleptic agents were most effective in pain relief, with a pain reduction of approximately 40mm on the VAS (Figure 35). Metoclopramide, NSAIDs, and opioids reduced pain by approximately 24mm. There were other, albeit less effective agents (e.g., DHE, triptans, and orphan drugs) which reduced pain by approximately 16-12 mm.

Overall, the strength of evidence for the mixed treatment analysis was low. Risk of bias was assessed as moderate and the results of this indirect analsysis were consistent.

Figure 35. Mixed treatment analysis of studies reporting pain score (VAS)



DHE = dihydroergotamine; mm = millmeters; NSAIDs = nonsteroidal anti-inflammatory drugs; PB = probability; VAS = Visual Analog Sscale

Table 31. Patient and study characteristics of trials comparing active combination therapy and active therapy

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Cicek, 2004, Turkey, RCT [110]	45 min, (4 hr)	G1: MET, n=196 (Vascular headache); 140 (tension headache), IM P + MET 10 mg IV G2: MET+PET, n=49, MET 10 mg IV + PET 50 mg IM G3: PET, n=49, IV placebo + PET 50 mg IM P: Placebo, n=48, NR IV/IM	Total: 38.8 (11.1) vascular headache; 42.1 (13.8) for tension headache; mean age of all subjects 40.2 (12.4), 7.1 (female to male ratio for vascular headache), 2.5 (in tension headache group),	G1: NR, NR G2: NR, NR P: NR, NR	1: pain intensity (VAS) 2: side effects
Corbo, 2001, U.S., RCT [81]	45 min, (24hr)	G1: MET+$MgSO_4$, n=21, 20 mg MET, 2 g $MgSO_4$ IV G2: MET + P, n=23, 20 mg IV	G1: 39 (12), 20 (95.2), NR G2: 37 (8), 22 (95.7), NR	G1: VAS: 80 mm (19), NR G2: VAS: 81 mm (23), NR	1: pain (VAS) 2: % of patients whose pain improved by >/= 50% from BL, percentage of patients with normal functional status at final rating in ED
Callaham, 1986, U.S., RCT[105]	90 min, (24 hr for pain relief and 48 hr for return visits)	G1: DHE+PCZ n=19, 0.75mg DHE+ 5mg PCZIV P: PCZ+P, n=15, 5mg PCZ + NR IV	G1: NR, NR, NR P: NR, NR, NR	Total: 10-pt scale: 6.3, NR	1: difference in pain scores (10-pt scale, 10 being the worst) 2: complete pain relief by end of study, optional tx by patient request: additional
Belgrade, 1989, U.S., RCT [107]	30 min (72 hr)	G1: MEP+HDZ, n=22, 75mg MEP + 50mg HDZIM G2: BUT, n=19, 2mg IM G3: MET, n=23, 1mg DHE + 10mg MET IV	G1: 33 (11), 13 (59.1), NR G2: 29 (9), 11 (57.9), NR G3: 29(8), 13 (61.9), NR	G1: Initial pain score (1-100): 82(18), NR G2: Initial pain score (1-100): 84(11), NR G3: Initial pain score (1-100): 83(19), NR	1: pain score improvement (scale of 1-100 where 100 is the worst possible pain) 2: blood pressure
Kelly, 1997,	120 min,	G1: CPZ, n=23, 12.5 mg	G1: 35 (NR), 17 (73.9),	G1: VAS: 75.7 (95% CI: 68.8,	1: mean pain scores (VAS)

Australia and New Zealand, RCT [32]	(NA)	IV G2: SUM, n=20, 6 mg IM	NR G2: 32 (NR), 12 (60.0) NR	82.6), NR G2: VAS: 74.6 (95% CI: 67.3, 81.9), NR	
Klapper, 1989, U.S., RCT [104]	30 min, (24 hr)	G1: MET+ DHE, n=11, 5-10mg MET and 0.75-1.0mg DHE IV G2: MET + DEX, n=9, 5-10mg MET and 6mg DEX IV P: Placebo, n=10, NR IV	G1: NR, NR, NR G2: NR, NR, NR P: NR, NR, NR	G1: NR, NR G2: NR, NR P: NR, NR	1: improvement by at least one unit (4-pt scale) 2: level of functioning (4-pt scale)
Klapper, 1991, U.S., RCT [98]	60 min (24 hr)	G1: KET, n=9, 60mg IM G2: DHE + MET, n=9, 1.0 mg DHE + 5mg MET IV	G1: NR, NR, NR G2: NR, NR, NR	G1: NR, NR G2: NR, NR	1: pain severity (pain severity scale: 0-3 with 3 being severe headache) 2: ability to function
Edwards, 2001, U.S., RCT [100]	1,2, and 4 hr, 4 hr (24 hr)	G1: MET + DHE, n=20, 10mg MET and 1 mg DHE IV G2: VAL, n=20, 500mg IV	G1: 43 (range 14-71), 18 (90.0), NR G2: 41 (range 14-73), 17 (85.0), NR	G1: Moderate: 8 (40.0), severe: 12 (60.0); 49.2hr (range 24-96), G2: Moderate: 6 (30.0), severe: 14 (70.0); 46.4hr (range 24-75)	1: headache relief 2: headache-associated nausea, photophobia and phonophobia, recurrence of headache, headache severity

BL = baseline; BUT = Butorphanol; CPZ = Chlorpromazine; DEX = Dexamethasone; DHE = Dihydroergotamine; ED = emergency department; G1 = group 1; G2 = group 2; G3 = group 3; HDZ = hydroxyzine; hr = hour(s); IM = intramuscular; IV = intravenous; KET = ketorolac; MEP = meperidine; MET = metoclopramide; $MgSO_4$ = magnesium sulphate; NR = not reported; P = placebo; PET = pethidine; RCT = randomized controlled trial; SD = standard deviation; SUM = sumatriptan; tx = treatment; VAL = valproate; VAS = Visual Analogue Scale

Key Question 2. Effectiveness of corticosteroids in the prevention of migraine relapse

Key Points

- Patients receiving dexamethasone plus standard abortive therapy were less likely to report recurrence of pain or headache up to 72 hours after discharge compared with placebo plus standard abortive therapy (moderate strength of evidence).

Description of Included Studies

Seven studies assessed the effectiveness of corticosteroids compared with placebo in the prevention of migraine relapse.[21-23,71,73,99,106] In every study, all patients were given standard abortive therapy after which they were administered either a placebo or IV dexamethasone prior to discharge. In the study by Fiesseler, participants were given either dexamethasone if IV access was obtained, or oral prednisone if there was no IV access.[99]

All trials were conducted in the ED. The mean ages of participant groups ranged from 32.6 to 38.0 years. The participants were predominantly female. All studies reported recurrence of headache or persistent pain free status post discharge. Three studies assessed participants at the time of discharge,[21,23,73] one assessed patients at 120 minutes after administration of the intervention,[22] and two studies did not assess patients in the ED.[99,106] One study contacted patients at 3 and 30 days post discharge,[71] and another assessed patients at 7 days after discharge.[23] The post-ED followup timepoints for the remaining studies ranged from 24 to 72 hours. See Table 33 for study and patient characteristics.

Three studies had an unclear risk of bias,[23,71,73,106] and four studies[21,22,73,99] had a low risk of bias (Appendix D).

Effectiveness Results

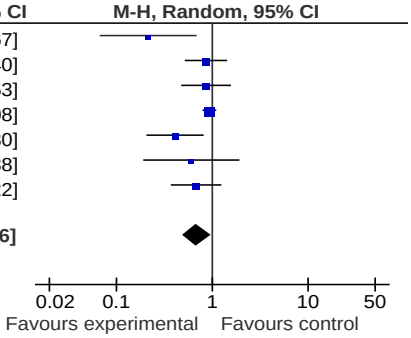
Headache recurrence (24-72 hours). We used the authors' definition of recurrence. In two studies,[21,106] recurrence was classified by severity of headache pain. For these studies, we extracted data for patients who reported severe headache (defined as having provoked a repeat physician visit and precluded return to normal activity). All studies reported on recurrence of pain or headache between 24 and 72 hours after discharge from the ED (Figure 36). The pooled results were statistically significant in favor of the corticosteroids (RR = 0.68; 95% CI: 0.49, 0.96; I^2 = 63%). Some of the heterogeneity resulted from the study by Baden, et al.[73] This study was stopped early for benefit.

We conducted a post hoc subgroup analysis to investigate differences in headache recurrence based on dosage of dexamethasone. Studies that used less than 15 mg (n = 4) of dexamethasone reported a weaker treatment effect (RR = 0.69; 95% CI: 0.40, 1.18; I^2 = 65%) than those using 15 mg or more (RR = 0.65; 95% CI: 0.43 to 0.99; I^2 = 37%). However, the difference between these two subgroups was not significant ($\chi 2$ = 2.01; df=1; p=0.16).

Figure 36. Recurrence of pain/headache (24-72 hours) in trials comparing dexamethasone and placebo

Study or Subgroup	Corticosteroid Events	Corticosteroid Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Baden 2006	3	31	14	31	6.7%	0.21 [0.07, 0.67]
Donaldson 2008	21	57	18	42	17.4%	0.86 [0.53, 1.40]
Fiesseler 2009	12	44	26	82	15.2%	0.86 [0.48, 1.53]
Friedman 2007	80	106	80	99	25.6%	0.93 [0.81, 1.08]
Innes 1999	9	49	22	49	13.3%	0.41 [0.21, 0.80]
Jones 2003	4	34	7	36	6.8%	0.61 [0.19, 1.88]
Rowe 2007	14	64	20	62	15.0%	0.68 [0.38, 1.22]
Total (95% CI)		**385**		**401**	**100.0%**	**0.68 [0.49, 0.96]**
Total events	143		187			

Heterogeneity: Tau² = 0.11; Chi² = 16.44, df = 6 (P = 0.01); I² = 63%
Test for overall effect: Z = 2.19 (P = 0.03)



Severe headaches (48-72 hours). In one study, participants were contacted to determine whether the occurrence of severe headaches differed between those who received dexamethasone and those who received the placebo.[73] Fewer people in the dexamethasone group had severe headaches; however, the results were not statistically significant (RR = 0.39; 95% CI: 0.13, 1.13).

Recurrence of pain (7 days). One study looked at recurrence of pain at 7 days.[23] While more individuals in the placebo group reported recurrent headache, the results were not statistically significant (RR = 0.70; 95% CI: 0.43, 1.14).

Recurrence of pain (30 days). One study compared headache recurrence at 30 days and found no difference between the dexamethasone and placebo (RR = 0.90; 95% CI: 0.58, 1.41).[71]

Table 32. Strength of evidence for corticosteroid versus placebo in prevention of headache recurrence

Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Corticosteroid vs. placebo	Headache recurrence at 24-72 hr (7; 801)	Moderate	Consistent	Direct	Precise	Moderate
	Headache recurrence at 7 days (1; 126)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache recurrence at 30 days (1; 98)	Moderate	Unknown	Direct	Imprecise	Insufficient

hr = hour(s); N = number; ROB = risk of bias

Table 33. Patient and study characteristics of trials comparing corticosteroid and placebo

Author, Year, Country Study design	Timepoints measured in the ED (Post ED followup)	Intervention, N randomized, dosage, route of administration	Mean age (SD), Females (%), White (%)	Description of migraine severity: mean (SD); duration of migraine prior to coming into ED	Primary outcomes; secondary outcomes
Baden, 2006, U.S., RCT[73]	before ED discharge, (48-72 hr)	G1: DEX, n=57 (total), 10 mg/ml IV P: Placebo, n=NR, 1 ml IV	G1: 34.5 (12.6), 18 (58.1), NR P: 32.6 (13.0), 17 (70.8), NR	G1: VAS: 75.0 mm (17.5), NR P: VAS: 77.3 mm (19.5), NR	1: recurrence of headache at 48-72 hr 2: headache severity at 48-72 hr, adverse events
Donaldson, 2008, U.S., RCT[71]	3 d, (30 d)	G1: DEX, n=62, 24 mg IV P: Placebo, n=53, NR IV	G1: 37.48, 54 (87.1), NR P: 35.17, 39 (73.6), NR	G1: 10-pt scale: 8.89, NR P: 10-pt scale: 8.76, NR	1: recurrence of headache at 3 and 30 d (4-pt ordinal scale: 0=no disability, 1=mild impairment, 2=moderate impairment, 3=severe impairment) 2: headache resolving in ED, satisfaction with ED visit, ED tx (medication received)
Fiesseler, 2009, U.S., RCT[99]	None in ED, (24-72 hr)	G1: DEX, n=48, 10mg IV P: Placebo, n=87, 1 ml IV	G1: 37 (10), 82 (87.2); Caucasian: 61 (64.9), Hispanic: 14 (14.9), Black: 8 (8.5), Asian: 4 (4.3), Other: 1 (1.1) P: 38 (10), 74 (85.1); Caucasian: 46 (52.9), Hispanic: 17 (19.5), Black: 9 (10.3), Asian: 2 (2.3), Other: 2 (2.3)	G1: VAS: 8.9, NR P: VAS: 8.9, NR	1: resolution of headache recurrence of symptoms after discharge from ED 2: use of rescue medication, recurrence of headache (score of at least 2 on the Likert pain scale), resolution of headache (score of 0 on the Likert pain scale)
Friedman, 2007, U.S., RCT[22]	120 min, (24 hr)	G1: DEX, n=106, 10 mg IV P: Placebo, n=99, 10 mg IV	G1: 36 (10), 87 (82.1); Latino: 72 (67.9), Black: 28 (26.4); White: 6 (5.7) P: 37 (11), 87 (87.9); Latino: 68 (68.7) Black: 21 (21.2); White: 2 (2.0)	G1: pain intensity (%): mild- 11, moderate- 25, severe- 64; 48 hr P: pain intensity (%): mild- 4, moderate- 28, severe- 68; 48 hr	1: persistent pain-free (4-pt scale) 2: no functional impairment after discharge, satisfaction with medication, pain-free at discharge, no functional impairment at discharge, adverse effects
Innes, 1999, Canada, RCT[21]	At discharge (results not reported by group), (48 hr)	G1: DEX, n=49, 24mg IV P: Placebo, n=49, NR IV	G1: 34 (9.9), 36 (73.5), NR P: 36 (8.6), 42 (85.7), NR	G1: VAS: 83 mm (IQR: 75-94), median: 12 hr (IQR: 5-28) P: VAS: 84 mm (IQR: 76-93), median: 11 hr (IQR: 6-30)	1: severe recurrent headache that provoked another physician visit or precluded normal activity (recurrent headaches classified as: class A severe, provoking another physician visit; class B severe, interfering with

					daily activity but not provoking a physician visit; class C mild requiring self-medication but not limiting activity; class D mild requiring no tx)
Jones, 2003, U.S., RCT[106]	None in ED, (48 hr)	G1: DEX, n=34, 20mg/2ml IV/IM P: Placebo, n=36, NR	G1: 35 (8.3), 27 (79.4), White: 30 (88.2) P: 36 (7.9), 28 (77.8), White: 31 (86.1)	G1: VAS score: 90mm, 39 (38) hr, NR P: VAS score: 88 mm, 37 (31) hr,	1: headache recurrence (4 class scale: A. Severe; provoked a repeat physician visit, B. Severe; precluded normal activity, C. Mild; analgesic necessary but no activity limitation, D. Mild; no treatment necessary, E. none) 2: adverse events
Rowe, 2007, Canada, RCT[23]	Prior to discharge from ED, (7 d)	G1: DEX, n=64 (total), 15 mg IV P: Placebo, n=62, NR IV	G1: 35 (11), 51 (80.0), NR P: 34.6 (10), 51 (82.3), NR	G1: VAS (median): 8, duration of headache >1day: 32/64 P: VAS (median): 8, duration of headache >1 day: 32/62	1: recurrence of pain at 72 hr (VAS) 2: recurrence of pain at 7 d (VAS)

d = day(s); DEX = dexamethasone; ED = emergency department; G1 = group 1; hr = hour(s); IM = intramuscular; IV = intravenous; NR = not reported; P = placebo; RCT = randomized controlled trial; SD = standard deviation; VAS = Visual Analogue Scale

Key Question 3. Short-term adverse effects of parenteral pharmacological interventions

Key Points

- Adverse effects were examined for individual arms of the trials, and not as comparative effectiveness comparisons. Strength of evidence was not graded.
- All reported adverse effects were considered minor and self-limiting.
- The risk of experiencing sedation following administration of metoclopramide and neuroleptic agents was common.
- Short-term side effects were commonly reported for patients receiving DHE. The most common side effects were skin and local reactions, sedation, digestive problems, nausea or vomiting, and chest symptoms.
- $MgSO_4$ was associated with high rates of skin flushing and local reactions.
- Side effects for triptans were infrequently reported; the most common side effect was local reactions.
- There were few short-term side effects reported for NSAIDs and opioids.

This section addresses the associated short-term adverse effects of parenteral pharmacological interventions used to treat acute migraine headaches and whether they differ across interventions. The results are presented by adverse effect categories (e.g., sedation, dizziness, vomiting). Adverse effects were examined for individual arms of the trials, and not as comparative effectiveness comparisons. When an intervention had more than one study reporting on any adverse effect, the results were pooled using a standard inverse variance random effects meta-analysis. For this reason, the proportion calculated by simply pooling the data may not be identical to the point estimate computed from the meta-analysis.

Vomiting

There were 25 unique studies that reported on the rates of vomiting, nausea, and emesis (Figure 37, Table 34).[23,32,48,52,53,55,56,59-61,69,71,74,76,86,89,93,95,97,100,102,103,106,107,110] When participants took the placebo, the risk of vomiting or experiencing nausea and emesis was 11 percent (95% CI: 7 to 16 percent). The risk for active agents ranged from 3 percent (95% CI: 0 to 7 percent) to 57 percent (95% CI: 41 to 72 percent).

Figure 37. Risk of nausea or vomiting reported in acute migraine trials

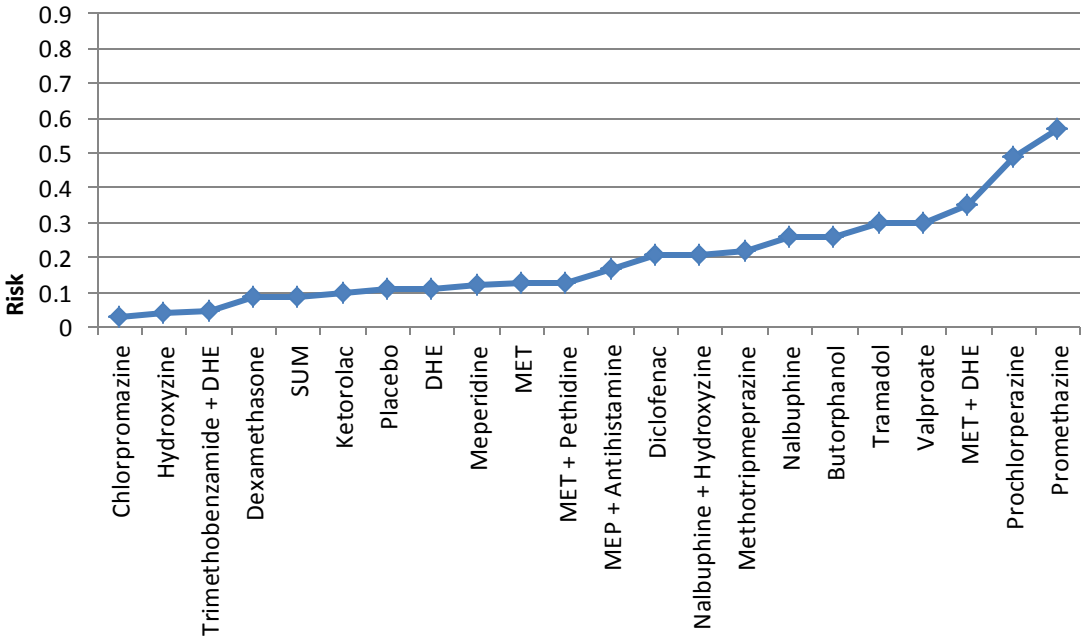


Table 34. Vomiting, nausea, emesis reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Cicek, 2004	5/83	0.06 [0.03, 0.13]
Tek, 1987	2/24	0.08, 0.02, 0.26]
Krymchantowski, 2003	1/12	0.08 [0.01, 0.35]
Wendt, 2006	15/193	0.08 [0.05, 0.12]
Bigal, 2002	10/30	0.33 [0.17, 0.51]
Mushet, 1996	11/79	0.14 [0.08, 0.23]
Cady, 1991	52/370	0.14 [0.11, 0.18]
Subtotal N=7	96/791	0.11 [0.07, 0.16]
Butorphanol		
Belgrade, 1989	5/19	0.26 [0.12, 0.49]
Subtotal N=1	5/19	0.26 [0.12, 0.49]
Chlorpromazine		
Cameron, 1995	1/47	0.02 [0.00, 0.11]
Lane, 1989	2/24	0.08 [0.02, 0.26]
Bigal, 2002	1/30	0.03 [0.01, 0.17]
Subtotal N=3	4/101	0.03 [0.00, 0.07]
Standard abortive therapy plus dexamethasone		
Rowe, 2008	4/64	0.06 [0.02, 0.15]
Donaldson, 2008	9/57	0.16 [0.09, 0.27]
Jones, 2003	2/34	0.06 [0.02, 0.19]
Subtotal N=3	15/155	0.09 [0.03, 0.14]
DHE		
Carleton, 1998	8/85	0.09 [0.05, 0.17]

Belgrade, 1989	7/21	0.33 [0.17, 0.55]
Winner, 1996	8/152	0.05 [0.03, 0.10]
Subtotal N=3	23/258	0.11 [0.02, 0.20]
Diclofenac		
Engindeniz, 2005	5/24	0.21 [0.09, 0.40]
Subtotal N=1	5/24	0.21 [0.09, 0.40]
Hydroxyzine		
Tek, 1987	1/23	0.04 [0.01, 0.21]
Subtotal N=1	1/23	0.04 [0.01, 0.21]
Ketorolac		
Duarte, 1992	3/25	0.12 [0.04, 0.30]
Larkin, 1992	1/15	0.07 [0.01, 0.30]
Subtotal N=2	4/40	0.10 [0.00, 0.19]
Meperidine		
Carleton, 1998	20/85	0.24 [0.16, 0.34]
Larkin, 1992	1/16	0.06 [0.01, 0.28]
Belgrade, 1989	1/22	0.05 [0.01, 0.22]
Subtotal N=3	22/123	0.12 [0.00, 0.25]
Meperidine plus antihistiamine		
Duarte, 1992	4/25	0.16 [0.06, 0.35]
Lane, 1989	2/22	0.09 [0.03, 0.28]
Stiell, 1991	10/37	0.27 [0.15, 0.43]
Subtotal N=3	16/84	0.17 [0.07, 0.28]
Methotrimeprazine		
Stiell, 1991	8/37	0.22 [0.11, 0.37]
Subtotal N=1	8/37	0.22 [0.11, 0.37]
Metoclopramide		
Cicek, 2004	6/85	0.07 [0.03, 0.15]
Jones, 1996	11/29	0.38 [0.23, 0.56]
Cameron, 1995	1/44	0.02 [0.00, 0.12]
Subtotal N=3	18/158	0.13 [0.00, 0.25]
Metoclopramide plus pethidine		
Cicek, 2004	11/84	0.13 [0.07, 0.22]
Subtotal N=1	11/84	0.13 [0.07, 0.22]
Metoclopramide plus DHE		
Edwards, 2001	7/20	0.35 [0.18, 0.57]
Subtotal N=1	7/20	0.35 [0.18, 0.57]
Nalbuphine		
Tek, 1987	6/23	0.26 [0.13, 0.46]
Subtotal N=1	6/23	0.26 [0.13, 0.46]
Nalbuphine plus hydroxyzine		
Tek, 1987	5/24	0.21 [0.09, 0.40]
Subtotal N=1	5/24	0.21 [0.09, 0.40]
Prochlorperazine		
Callan, 2008	17/35	0.49 [0.33, 0.64]
Jones, 1996	14/28	0.50 [0.33, 0.67]
Subtotal N=2	31/63	0.49 [0.38, 0.61]
Promethazine		

Callan, 2008	20/35	0.57 [0.41, 0.72]
Subtotal N=1	20/35	0.57 [0.41, 0.72]
Sumatriptan		
Friedman, 2006	6/20	0.30 [0.15, 0.52]
Kelly, 1997	1/20	0.05 [0.01, 0.24]
Wendt, 2006	28/384	0.07 [0.05, 0.10]
Mushet, 1996	10/79	0.13 [0.07, 0.22]
Akpunonu, 1995	8/88	0.09 [0.05, 0.17]
Cady, 1991	68/547	0.12 [0.10, 0.15]
Winner, 1996	6/158	0.04 [0.02, 0.08]
Subtotal N=7	127/1296	0.09 [0.05, 0.13]
Tramadol		
Engindeniz, 2005	7/23	0.30 [0.16, 0.51]
Subtotal N=1	7/23	0.30 [0.16, 0.51]
Trimethobenzamide plus DHE		
Friedman, 2006	1/20	0.05 [0.01, 0.24]
Subtotal N=1	1/20	0.05 [0.01, 0.24]
Valproate		
Edwards, 2001	6/20	0.30 [0.15, 0.52]
Subtotal N=1	6/20	0.30 [0.15, 0.52]

CI = confidence interval; DHE = dihydroergotamine

Sedation/somnolence

There were 24 unique studies that reported the development of sedation/somnolence including drowsiness and decreased levels of consciousness (Figure 38, Table 35).[21,22,48,52,55,59-62,69,70,74,80-82,86,89,92,93,97,102,106,107,110] The risk of developing sedation/somnolence as a result of taking placebo was 8 percent (95% CI: 3 to 12 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 common (17 percent each).

Figure 38. Risk of sedation reported in migraine trials

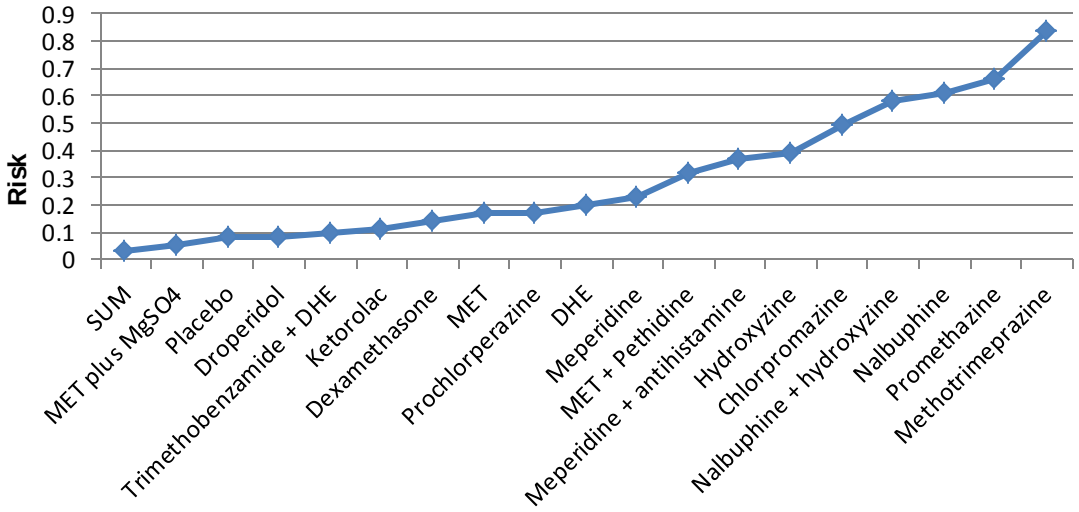


Table 35. Sedation/somnolence reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Cicek, 2004	4/83	0.05 [0.02, 0.12]
McEwen, 1987	6/17	0.35 [0.17, 0.59]
Tek, 1987	4/24	0.17 [0.07, 0.36]
Wendt, 2006	4/193	0.02 [0.01, 0.05]
Bigal, 2002	10/30	0.33 [0.19, 0.51]
Cady, 1991	8/370	0.02 [0.01, 0.04]
Jones, 2003	4/36	0.11 [0.04, 0.25]
Subtotal N=7	40/753	0.08 [0.03, 0.12]
Chlorpromazine		
Cameron, 1995	8/47	0.17 [0.09, 0.30]
Lane, 1989	5/24	0.21 [0.09, 0.40]
McEwen, 1987	15/19	0.79 [0.57, 0.91]
Bigal, 2002	24/30	0.80 [0.63, 0.90]
Subtotal N=4	52/120	0.49 [0.14, 0.84]
Standard abortive therapy plus Dexamethasone		
Friedman, 2007	3/106	0.03 [0.01, 0.08]
Innes, 1999	12/49	0.24 [0.15, 0.38]
Jones, 2003	6/34	0.18 [0.08, 0.34]
Subtotal N=3	21/189	0.14 [0.00, 0.29]
DHE		
Carleton, 1998	17/85	0.20 [0.13, 0.30]
Subtotal N=1	17/85	0.20 [0.13, 0.30]
Droperidol		
Richman, 2002	1/15	0.07 [0.01, 0.30]
Miner, 2001	7/82	0.09 [0.04, 0.17]
Subtotal N=2	8/97	0.08 [0.03, 0.14]
Hydroxyzine		
Tek, 1987	9/23	0.39 [0.22, 0.59]
Subtotal N=1	9/23	0.39 [0.22, 0.59]
Ketorolac		
Duarte, 1992	2/25	0.08 [0.02, 0.25]

Larkin, 1992	3/15	0.20 [0.07, 0.45]
Subtotal N=2	5/40	0.11 [0.01, 0.22]
Meperidine		
Richman, 2002	2/14	0.14 [0.04, 0.40]
Carleton, 1998	23/85	0.27 [0.19, 0.37]
Larkin, 1992	2/16	0.13 [0.03, 0.36]
Belgrade, 1989	4/22	0.18 [0.07, 0.39]
Cicek, 2004 (Pethidine)	22/84	0.26 [0.18, 0.36]
Subtotal N=5	53/221	0.23 [0.17, 0.28]
Meperidine plus Antihistiamine		
Duarte, 1992	7/25	0.28 [0.14, 0.48]
Stiell, 1991	24/37	0.65 [0.49, 0.78]
Lane, 1989	4/22	0.18 [0.07, 0.39]
Subtotal N=3	35/84	0.37 [0.08, 0.66]
Methotrimeprazine		
Stiell, 1991	31/37	0.84 [0.69, 0.92]
Subtotal N=1	31/37	0.84 [0.69, 0.92]
Metoclopramide		
Friedman, 2008	5/38	0.13 [0.06, 0.27]
Cicek, 2004	17/85	0.20 [0.13, 0.30]
Jones, 1996	5/29	0.17 [0.08, 0.35]
Cameron, 1995	7/44	0.16 [0.08, 0.29]
Subtotal N=4	34/196	0.17 [0.12, 0.22]
Metoclopramide plus Pethidine		
Cicek, 2004	27/84	0.32 [0.23, 0.43]
Subtotal N=1	27/84	0.32 [0.23, 0.43]
Metoclopramide plus $MgSO_4$		
Corbo, 2001	1/21	0.05 [0.01, 0.23]
Subtotal N=1	1/21	0.05 [0.01, 0.23]
Nalbuphine		
Tek, 1987	14/23	0.61 [0.41, 0.78]
Subtotal N=1	14/23	0.61 [0.41, 0.78]
Nalbuphine plus Hydroxyzine		
Tek, 1987	14/24	0.58 [0.39, 0.76]
Subtotal N=1	14/24	0.58 [0.39, 0.76]
Prochlorperazine		
Callan, 2008	14/35	0.40 [0.26, 0.56]
Friedman, 2008	6/39	0.15 [0.07, 0.30]
Miner, 2001	1/86	0.01 [0.00, 0.06]
Jones, 1996	5/28	0.18 [0.08, 0.36]
Jones, 1989	7/42	0.17 [0.08, 0.31]
Subtotal N=5	33/230	0.17 [0.04, 0.30]
Promethazine		
Callan, 2008	25/35	0.66 [0.49, 0.79]
Subtotal N=1	25/35	0.66 [0.49, 0.79]
Sumatriptan		
Friedman, 2006	2/20	0.10 [0.03, 0.30]
Wendt, 2006	11/384	0.03 [0.02, 0.05]
Cady, 1991	15/547	0.03 [0.02, 0.04]
Subtotal N=3	28/951	0.03 [0.02, 0.04]
Trimethobenzamide plus DHE		
Friedman, 2006	2/20	0.10 [0.03, 0.30]
Subtotal N=1	2/20	0.10 [0.03, 0.30]

CI = confidence interval; DHE = dihydroergotamine; $MgSO_4$ = magnesium sulphate;

Dizziness

Twenty-two unique studies reported dizziness as an adverse effect. Included in this category are postural hypertension, syncope, relative hypotension, orthostatic hypotension, fainting, head rushes and dizzy spells (Figure 39, Table 36).[21,22,48,52,53,55,59-62,66,70,71,81,92,93,95,102,103,106,107,110] The risk of becoming dizzy in those who received placebo was 4 percent (95% CI: 2 to 5 percent). The risk in those who received an active agent ranged from 2 percent (95% CI: 1 to 8 percent) to 32 percent (95% CI: 20 to 49 percent).

Figure 39. Risk of dizziness reported in acute migraine trials

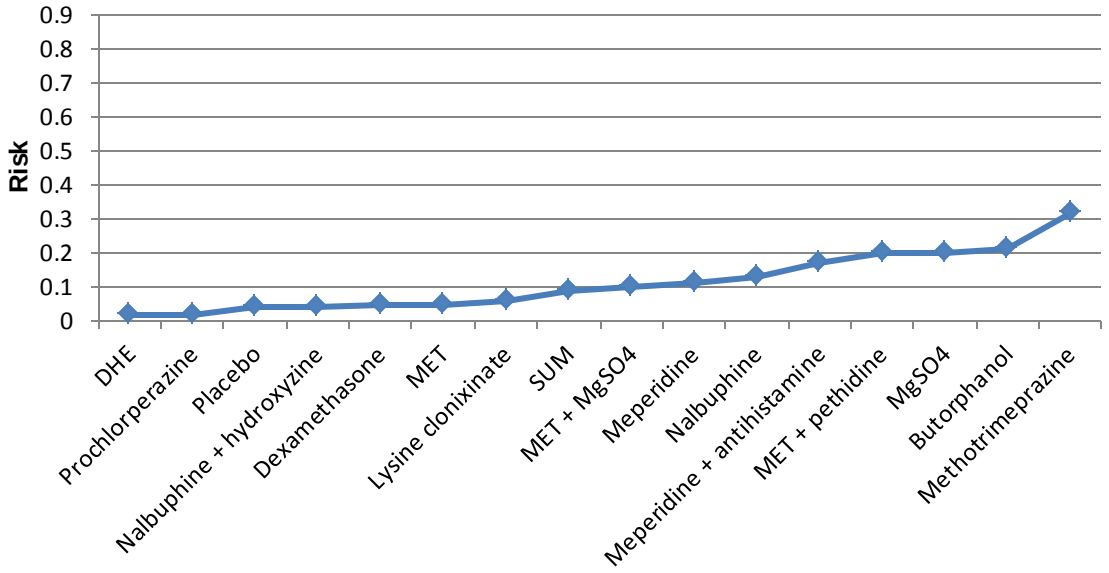


Table 36. Dizziness reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Cicek, 2004	1/83	0.01 [0.00, 0.07]
McEwen, 1987	3/17	0.18 [0.06, 0.41]
Krymchantowski, 2003	1/12	0.08 [0.01, 0.35]
Wendt, 2006	10/193	0.05 [0.03, 0.09]
Bigal, 2002	1/30	0.03 [0.01, 0.17]
Mushet, 1996	2/79	0.03 [0.01, 0.09]
Cady, 1991	15/370	0.04 [0.02, 0.07]
Subtotal N=7	33/784	0.04 [0.02, 0.05]
Butorphanol		
Belgrade, 1989	4/19	0.21 [0.09, 0.43]
Subtotal N=1	4/19	0.21 [0.09, 0.43]
Standard abortive therapy plus dexamethasone		
Donaldson, 2008	9/57	0.16 [0.09, 0.43]
Friedman, 2007	3/106	0.03 [0.01, 0.08]
Innes, 1999	2/49	0.04 [0.01, 0.14]
Jones, 2003	1/34	0.03 [0.01, 0.15]
Subtotal N=4	15/246	0.05 [0.01, 0.10]
DHE		
Carleton, 1998	2/85	0.02 [0.01, 0.08]

Subtotal N=1	2/85	0.02 [0.01, 0.08]
Lysine clonixinate		
Krymchantowski, 2003	1/17	0.06 [0.01, 0.27]
Subtotal N=1	1/17	0.06 [0.01, 0.27]
Meperidine		
Carleton, 1998	13/85	0.15 [0.09, 0.24]
Belgrade, 1989	1/22	0.05 [0.01, 0.22]
Subtotal N=2	14/107	0.11 [0.00, 0.21]
Meperidine plus Antihistamine		
Stiell, 1991	11/37	0.30 [0.17, 0.46]
Lane, 1989	1/22	0.05 [0.01, 0.22]
Subtotal N=2	12/59	0.17 [0.00, 0.41]
Methotrimeprazine		
Stiell, 1991	12/37	0.32 [0.20, 0.49]
Subtotal N=1	12/37	0.32 [0.20, 0.49]
Metoclopramide		
Friedman, 2008	2/38	0.05 [0.01, 0.17]
Cicek, 2004	3/85	0.04 [0.01, 0.10]
Corbo, 2001	1/23	0.04 [0.01, 0.21]
Cameron, 1995	4/44	0.09 [0.04, 0.21]
Subtotal N=4	10/190	0.05 [0.01, 0.08]
Metoclopramide plus pethidine		
Cicek, 2004	17/84	0.20 [0.13, 0.30]
Subtotal N=1	17/84	0.20 [0.13, 0.30]
Metoclopramide plus $MgSO_4$		
Corbo, 2001	2/21	0.10 [0.03, 0.29]
Subtotal N=1	2/21	0.10 [0.03, 0.29]
$MgSO_4$		
Demirkaya, 2001	3/15	0.20 [0.07, 0.45]
Subtotal N=1	3/15	0.20 [0.07, 0.45]
Nalbuphine		
Tek, 1987	3/23	0.13 [0.05, 0.32]
Subtotal N=1	3/23	0.13 [0.05, 0.32]
Nalbuphine plus hydroxyzine		
Tek, 1987	1/24	0.04 [0.01, 0.20]
Subtotal N=1	1/24	0.04 [0.01, 0.20]
Prochlorperazine		
Jones, 1989	1/42	0.02 [0.00, 0.12]
Subtotal N=1	1/42	0.02 [0.00, 0.12]
Sumatriptan		
Wendt, 2006	40/384	0.10 [0.08, 0.14]
Mushet, 1996	3/79	0.04 [0.01, 0.11]
Akpunonu, 1995	8/88	0.09 [0.05, 0.17]
Cady, 1991	65/547	0.12 [0.09, 0.15]
Subtotal N=4	116/1098	0.09 [0.06, 0.12]

CI = confidence interval; DHE = dihydroergotamine; $MgSO_4$ = magnesium sulphate

Local reaction

There were 13 studies that measured local reactions including pain or swelling at the injection site and IV site irritation (Figure 40, Table 37).[23,48,52,53,55,56,61,71,81,84,93,95,106] The risk in those who received placebo was 19 percent (95% CI: 13 to 24 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).

Figure 40. Risk of local reaction reported in acute migraine trials

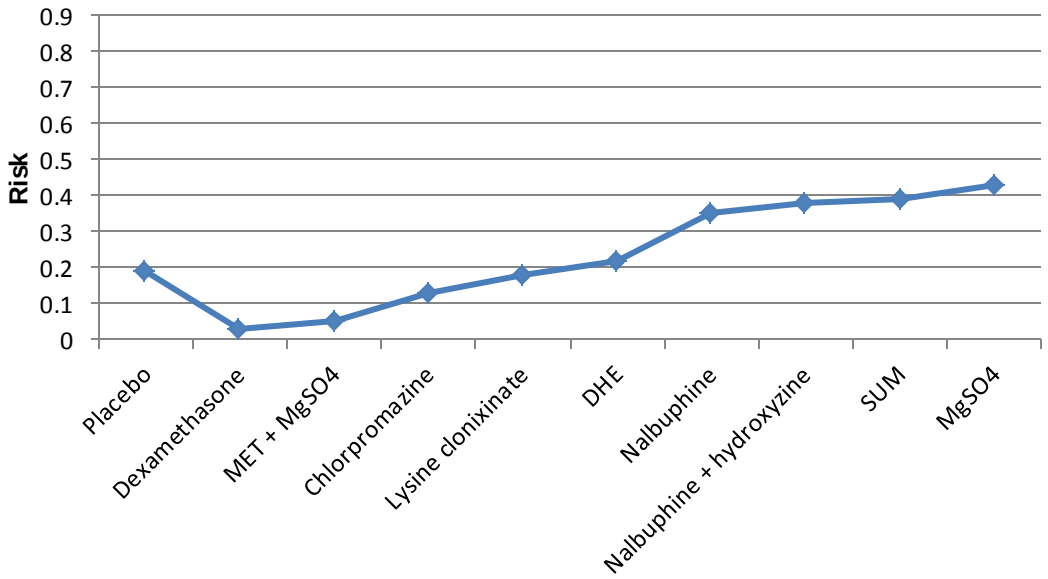


Table 37. Local reaction reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Tek, 1987	4/24	0.17 [0.07, 0.36]
Wendt, 2006	28/193	0.15 [0.10, 0.20]
Mushet, 1996	14/79	0.18 [0.11, 0.28]
Cady, 1991	88/370	0.24 [0.20, 0.28]
Subtotal N=4	134/666	0.19 [0.13, 0.24]
Chlorpromazine		
Lane, 1989	3/24	0.13 [0.04, 0.31]
Subtotal N=4	3/24	0.13 [0.04, 0.31]
Standard abortive therapy plus Dexamethasone		
Rowe, 2008	2/64	0.03 [0.01, 0.11]
Donaldson, 2008	2/57	0.04 [0.01, 0.12]
Jones, 2002	1/34	0.03 [0.01, 0.15]
Subtotal N=3	5/155	0.03 [0.00, 0.06]
DHE		
Carleton, 1998	6/85	0.07 [0.03, 0.15]
Winner, 1996	57/152	0.38 [0.30, 0.45]
Subtotal N=2	63/237	0.22 [0.00, 0.52]
Lysine clonixinate		
Krymchantowski, 2003	3/17	0.18 [0.06, 0.41]
Subtotal N=1	3/17	0.18 [0.06, 0.41]
Metoclopramide plus $MgSO_4$		
Corbo, 2001	1/21	0.05 [0.01, 0.23]
Subtotal N=1	1/21	0.05 [0.01, 0.23]
$MgSO_4$		
Ginder, 2000	3/7	0.43 [0.16, 0.75]
Subtotal N=1	3/7	0.43 [0.16, 0.75]

Nalbuphine		
Tek, 1987	8/23	0.35 [0.19, 0.55]
Subtotal N=1	8/23	0.35 [0.19, 0.55]
Nalbuphine plus Hydroxyzine		
Tek, 1987	9/24	0.38 [0.21, 0.57]
Subtotal N=1	9/24	0.38 [0.21, 0.57]
Sumatriptan		
Wendt, 2006	165/384	0.43 [0.38, 0.48]
Mushet, 1996	27/79	0.34 [0.25, 0.45]
Cady, 1991	321/547	0.59 [0.55, 0.63]
Winner, 1996	28/158	0.18 [0.13, 0.24]
Subtotal N=4	541/1168	0.39 [0.20, 0.57]

CI = confidence interval; DHE = dihydroergotamine; IV = intravenous; $MgSO_4$ = magnesium sulphate

Skin reactions

There were nine studies that measured skin reactions to the interventions administered (Figure 41, Table 38).[32,52,53,55,66,78,81,107,110] Included in this category were 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).

Figure 41. Risk of skin reaction reported in acute migraine trials

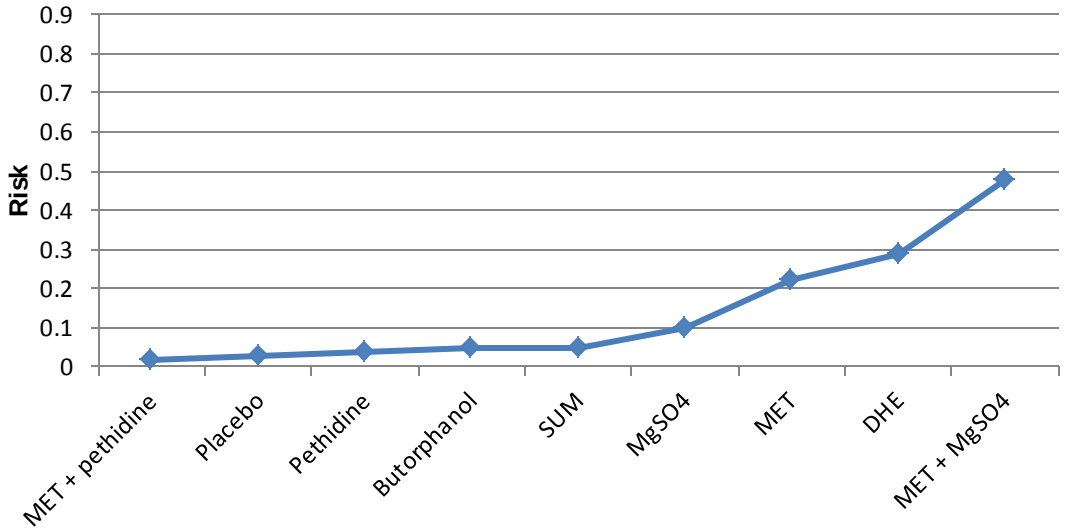


Table 38. Skin reaction reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Wendt, 2006	7/193	0.04 [0.02, 0.07]
Mushet, 1996	2/79	0.03 [0.01, 0.09]
Subtotal N=2	9/272	0.03 [0.01, 0.06]
Butorphanol		

Belgrade, 1989	1/19	0.05 [0.01, 0.25]
Subtotal N=1	1/19	0.05 [0.01, 0.25]
DHE		
Belgrade, 1989	6/21	0.29 [0.14, 0.50]
Subtotal N=1	6/21	0.29 [0.14, 0.50]
Metoclopramide		
Corbo, 2001	5/23	0.22 [0.10, 0.42]
Subtotal N=1	5/23	0.22 [0.10, 0.42]
Metoclopramide plus Pethidine		
Cicek, 2004	2/84	0.02 [0.01, 0.08]
Subtotal N=1	2/84	0.02 [0.01, 0.08]
Metoclopramide plus $MgSO_4$		
Corbo, 2001	10/21	0.48 [0.28, 0.68]
Subtotal N=1	10/21	0.48 [0.28, 0.68]
$MgSO_4$		
Demirkaya, 2001	2/15	0.13 [0.04, 0.38]
Cete, 2004	3/36	0.08 [0.03, 0.22]
Subtotal N=2	5/51	0.10 [0.01, 0.18]
Pethidine		
Cicek, 2004	3/84	0.04 [0.01, 0.10]
Subtotal N=1	3/84	0.04 [0.01, 0.10]
Sumatriptan		
Kelly, 1997	1/20	0.05 [0.01, 0.24]
Wendt, 2006	10/384	0.03 [0.01, 0.05]
Mushet, 1996	4/79	0.05 [0.02, 0.12]
Cady, 1991	36/547	0.07 [0.05, 0.09]
Subtotal N=4	51/1030	0.05 [0.02, 0.07]

CI = confidence interval; DHE = dihydroergotamine; $MgSO_4$ = magnesium sulphate

Extrapyramidal symptoms

Six studies reported extrapyramidal symptoms as a result of treatment.[53,60,74,77,78,82] Included in this category are dystonic reactions, stiff neck, abnormal movements, and/or muscle twitching. The symptoms varied across studies and included muscle cramps,[53] dystonia,[60,82] muscle twitching,[60] stiffness or abnormal movements,[77] and stiff neck.[74] Results for akathsia are presented under KQ 4. See Table 39 for a summary of the results.

Table 39. Extrapyramidal symptoms reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Mushet, 1996	1/79	0.01 [0.00, 0.07]
Subtotal N=1	1/79	0.01 [0.00, 0.07]
Droperidol		
Miner, 2001	1/82	0.01 [0.00, 0.07]
Subtotal N=1	1/82	0.01 [0.00, 0.07]
Methotrimeprazine		
Stiell, 1991	3/37	0.08 [0.03, 0.21]
Subtotal N=1	3/37	0.08 [0.03, 0.21]

Metoclopramide		
Friedman, 2005	3/40	0.08 [0.03, 0.20]
Cete, 2004	1/37	0.03 [0.00, 0.14]
Subtotal N=2	4/77	0.04 [0.00, 0.10]
Sumatriptan		
Friedman, 2006	3/20	0.15 [0.05, 0.36]
Friedman, 2005	7/38	0.18 [0.09, 0.33]
Mushet, 1996	2/79	0.03 [0.01, 0.09]
Subtotal N=3	12/137	0.11 [0.00, 0.22]

CI = confidence interval

Chest symptoms

Five studies assessed chest symptoms, which included palpitations, arrhythmia, and/or irregular heartbeat.[32,52,53,56,103] See Table 40 for a summary of results.

Table 40. Chest symptoms reported in migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Wendt, 2006	2/193	0.01 [0.00, 0.04]
Subtotal N=1	2/193	0.01 [0.00, 0.04]
Chlorpromazine		
Kelly, 1997	1/23	0.04 [0.01, 0.21]
Subtotal N=1	1/23	0.04 [0.01, 0.21]
DHE		
Winner, 1996	14/152	0.09 [0.06, 0.15]
Subtotal N=1	14/152	0.09 [0.06, 0.15]
Sumatriptan		
Wendt, 2006	20/384	0.05 [0.03, 0.08]
Mushet, 1996	5/79	0.06 [0.03, 0.14]
Akpunonu, 1995	5/88	0.06 [0.02, 0.13]
Winner, 1996	9/158	0.06 [0.03, 0.10]
Subtotal N=4	39/709	0.05 [0.04, 0.07]

CI = confidence interval; DHE = dihydroergotamine

Anxiety

Anxiety and related adverse effects, including mood change, moodiness, agitation, insomnia were reported in five unique studies.[52,55,69,71,73] See Table 41 for a summary of results.

Table 41. Anxiety reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Cady, 1991	16/370	0.04 [0.03, 0.07]
Subtotal N=1	16/370	0.04 [0.03, 0.07]
Standard abortive therapy plus Dexamethasone		
Donaldson, 2008	3/57	0.05 [0.02, 0.14]
Baden, 2006	1/31	0.03 [0.01, 0.16]
Subtotal N=2	4/88	0.04 [0.00, 0.09]
Prochlorperazine		
Callan, 2008	13/35	0.37 [0.23, 0.54]
Subtotal N=1	13/35	0.37 [0.23, 0.54]

Promethazine		
Callan, 2008	8/35	0.23 [0.12, 0.39]
Subtotal N=1	8/35	0.23 [0.12, 0.39]
Sumatriptan		
Wendt, 2006	4/384	0.01 [0.00, 0.03]
Cady, 1991	6/547	0.01 [0.01, 0.02]
Subtotal N=2	10/931	0.01 [0.00, 0.02]

CI = confidence interval

Digestion issues

Two studies assessed digestion issues that were attributed to the interventions.[22,48] Included in this category were any reports on dyspepsia, heartburn, epigastric discomfort, and/or diarrhea. See Table 42 for a summary of results.

Table 42. Digestion issues reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Friedman, 2007	3/99	0.03 [0.01, 0.09]
Subtotal N=1	3/99	0.03 [0.01, 0.09]
DHE		
Carleton, 1998	10/85	0.12 [0.07, 0.20]
Subtotal N=1	10/85	0.12 [0.07, 0.20]
Meperidine		
Carleton, 1998	4/85	0.05 [0.02, 0.11]
Subtotal N=1	4/85	0.05 [0.02, 0.11]

CI = confidence interval; DHE = dihydroergotamine

Emergence reactions

Two studies reported emergence reactions that resulted from the administration of placebo and sumatriptan.[32,53] Included in this category were unpleasant dreams, and/or nightmares. See Table 43 for a summary of the results.

Table 43. Emergence reactions reported in acute migraine trials

Author, Year	n/N	Risk (95% CI)
Placebo		
Mushet, 1996	2/79	0.03 [0.01, 0.09]
Subtotal N=1	2/79	0.03 [0.01, 0.09]
Sumatriptan		
Kelly, 1997	1/20	0.05 [0.01, 0.24]
Mushet, 1996	1/79	0.01 [0.00, 0.07]
Subtotal N=2	2/99	0.02 [0.00, 0.05]

CI = confidence interval

Key Question 4. Development of akathisia

Key Points

- No conclusions can be drawn regarding the development of akathisia when an anticholinergic is added to metoclopramide or phenothiazines (insufficient strength of evidence).

- Based on a mixed treatment analysis, there is no statistically significant difference in the development of akathisia between neuroleptics and metoclopramide.

One study examined the differences in the development of akathisia when metoclopramide or phenothiazines were used with anticholinergic agents (Table 6).[70] In this study, participants were administered either prochlorperazine or metoclopramide, both accompanied by 25 mg of intravenous diphenhydramine.[70] The difference in rates of akathisia between the two groups was not statistically significant (OR = 1.50; 95% CI: 0.24, 9.52) (Table 44).

Table 44. Strength of evidence for the development of akathisia when anticholinergic agents are added to metoclopramide or phenothiazines

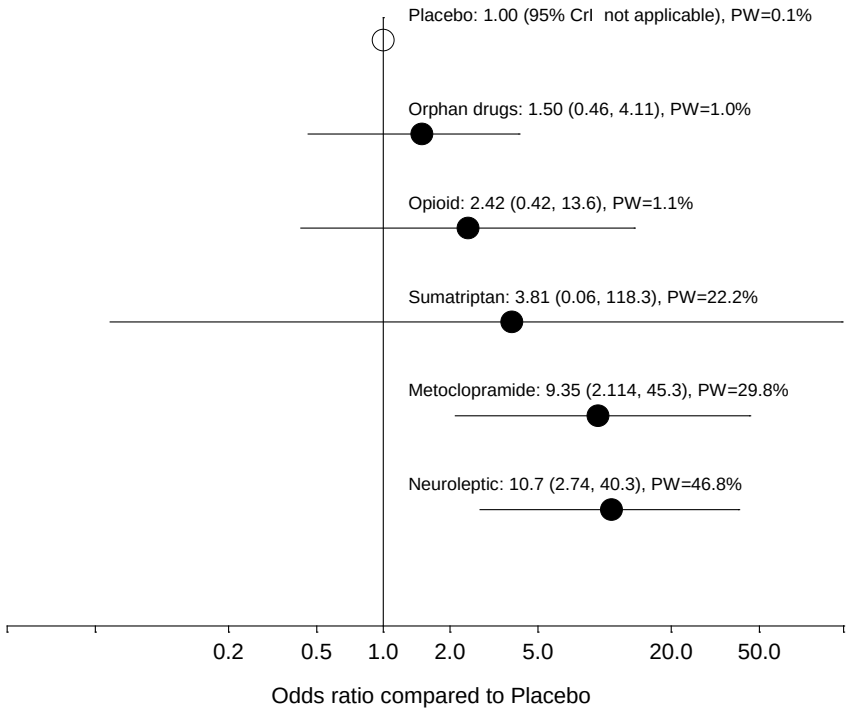
Comparison	Outcome (N studies; N patients)	Strength of evidence domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Metoclopramide+ anticholinergic vs. Phenothiazine+ anticholinergic	Akathisia (1; 77)	Moderate	Unknown	Direct	Imprecise	Insufficient

N = number; ROB = risk of bias

In another study, participants were administered prochlorperazine plus diphenhydramine or prochlorperazine alone (Table 9).[29] The authors were unable to identify a difference in the development of akathisia symptoms with the addition of diphenhydramine (OR = 0.46; 95% CI: 0.17, 1.28).

We conducted a post hoc mixed treatment analysis of 15 studies that reported akathisia as a side effect. In addition to neuroleptics and metoclopramide, other interventions included opioids, sumatriptan, and orphan drugs (i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide). The results show that there is no statistically significant increase in akathisia when using agents except neuroleptic agents and metoclopramide. The results also show that there is no statistically significant difference in the risk of akathisia between neuroleptics and metoclopramide. The odds of experiencing akathisia symptoms following administration of these drugs is in the range of 10 times greater than with placebo (Figure 42).

Figure 42. Mixed treatment analysis of studies that report akathisia as a side effect



Key Question 5. Effectiveness and safety of parenteral pharmacological interventions in different subgroups

No studies presented results for the subgroups race, and duration of headaches; only one study reported on subgroup differences related to sex.[23]

The detailed summary of results of the non-response data are available in Appendix E. Failure to respond was either defined by the authors (often in multiple ways), or described as not reaching a pain free status during the ED visit. The most commonly reported outcome was some measure of non-response; 32 (46 percent) reported both non-response and pain free status. There were variable definitions of non-response found in the acute migraine literature. The cut point for the reduction in pain indicating "response" varied widely (e.g., 90 percent, 45 percent). Time to assessment for response varied (e.g., end of treatment, 30-60 minutes, and up to 6 hours). Many studies failed to report the final scores in sufficient detail to determine which patients responded.

Few studies followed up their patients after discharge, so it is difficult to determine the relationship between non-response and relapse outcomes. One study[62] found that patients (treatment and placebo) who achieved complete relief in the ED had no recurrence of headache within 48 hours. Another study specifically reported no difference in response between men and women at 24-48 hours after ED discharge; however, this study was focused on prevention, not the acute treatment.[23]

Key Question 6. Subpopulations in studies assessing the effectiveness of corticosteroids in prevention of migraine relapse

Several studies conducted an a priori subgroup analysis based on duration of headache.[22] In the first, the authors compared patients who had an acute migraine lasting longer than 72 hours (n = 45) versus patients with headache duration of 72 hours or less (n = 160). The primary outcome was persistent pain free (i.e., pain resolved completely by 2 hours and not recurring through 24 hours followup). For patients with longer headache duration, more patients receiving dexamethasone were persistently pain free compared with those receiving placebo (OR = 4.1; 95% CI: 0.9, 18). For patients with shorter headache duration, there was no difference between the groups (OR = 1.0; 95% CI: 0.5, 2.2).

In the second study, relapse was explored using the median headache duration (24 hours) from the study sample as the cut point.[23] Among patients whose headache had lasted more than 24 hours prior to ED presentation, the odds of relapse for those treated with dexamethasone was 0.3 (95% CI: 0.1, 0.8); dexamethasone did not reduce relapses among patients whose headache had lasted less than 24 hours (OR=1.7; 95% CI: 0.5, 5.8). Finally, using a post hoc regression analysis, Innes et al. demonstrated an association between increased headache duration and severe recurrent headache, suggesting that the relative risk of recurrent severe headache increases by about 1 percent per hour of headache duration.[21] Overall, all authors concluded that a dose of IV dexamethasone administered in the ED may be more effective for patients with prolonged migraine headache.

One trial conducted a subgroup analysis based on residual pain at discharge (VAS > 2) compared with patients with better response to therapy (VAS $\leq$ 2).[23] After adjusting for experimental treatment, only residual pain as measured by the VAS was a significant predictor of relapse. Patients with a VAS score > 2 at ED discharge were at a higher risk of relapse than those whose pain was assessed at $\leq$ 2 at discharge (adjusted OR=2.4; 95% CI: 1.1, 5.4).

Summary and Discussion

Key Findings and Strength of Evidence

This report provides a comprehensive synthesis of the evidence on 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 or an equivalent setting. The strength of the body of evidence for key effectiveness outcomes is summarized by intervention in Table 45.

For the majority of studies pain relief or severity was the primary outcome. There were nine different classes of drugs investigated in 69 studies. The interventions included antiemetics, neuroleptics, ergotamines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, a group of agents collectively referred to as orphan agents (i.e. magnesium sulphate [$MgSO_4$], valproate), and triptans.

Data were provided primarily from randomized controlled trials (RCTs). Risk of bias assessment showed that 30 percent of the trials had low risk of bias, and 58 percent had unclear risk of bias. Sample sizes varied, with an overall median of 64 patients per study (interquartile range [IQR]: 40 to 100).

Generally, active interventions compared with placebo were more effective in relieving pain and reducing headache recurrence. In the mixed treatment analysis of pain relief, there was a clear indication that combinations of anti-migraine medications and the neuroleptics out-performed other agents. The pain relief data must be weighed carefully with the data on side effects, especially akathisia. The following is a summary of the evidence for the six Key Questions.

Key Question 1: Effectiveness of parenteral interventions versus placebo or an active treatment

The findings for pain relief and headache recurrence are presented for each intervention in Table 45.

Metoclopramide was compared with placebo in six trials and with other active treatments in nine trials. Metoclopramide was significantly more effective than placebo for pain relief (moderate strength of evidence). There was insufficient evidence for headache recurrence. Results for pain relief were inconsistent when comparing metoclopramide monotherapy with other active treatments (excluding neuroleptics) (low strength of evidence). Metoclopramide was generally less effective than neuroleptics for pain relief although this wasn't consistent across studies (low strength of evidence). The mixed treatment analysis demonstrated that as monotherapy, metoclopramide was similarly effective to opioids and NSAIDs for pain relief (low strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing metoclopramide with other active agents including neuroleptics.

Neuroleptics were compared with placebo in 7 trials and with other active treatments in 17 trials. Neuroleptics were more effective than placebo for pain relief (moderate strength of evidence) and for headache recurrence (low strength of evidence). Neuroleptic agents were generally more effective than other active treatments for change in pain

intensity (moderate strength of evidence). There was no significant difference between neuroleptics and active comparators with respect to headache recurrence (low strength of evidence). The mixed treatment analysis demonstrated that monotherapy with neuroleptic agents was one of the more effective treatment options.

NSAIDs were compared with placebo in two trials and with other active treatments in nine trials. NSAIDs were more effective than placebo for pain relief (moderate strength of evidence) and headache recurrence (low strength of evidence). Results were mixed for NSAIDs compared with other active agents for pain relief (low strength of evidence); however, the mixed treatment analysis demonstrated that NSAIDs were similarly effective to opioids and metoclopramide (low strength of evidence). There was insufficient strength of evidence for headache recurrence when NSAIDs were compared with active agents.

Opioids were compared with placebo in 3 trials and with other active treatments in 12 trials. Opioids were more effective than placebo for pain relief (moderate strength of evidence). Results were mixed for opioids compared with other active agents for pain relief (low strength of evidence); however, the mixed treatment analysis demonstrated that opioids were similarly effective to NSAIDs and metoclopramide (low strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing opioids and other active agents.

Dihydroergotamine (DHE) was compared with other active treatments in five trials. Results were mixed for pain relief (low strength of evidence). DHE was more effective in preventing headache recurrence compared with sumatriptan (low strength of evidence). The mixed treatment analysis demonstrated that DHE monotherapy was similarly effective to orphan drugs and anti-nauseants, but less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence).

Triptans were compared with placebo in six trials and with other active agents in six trials. Sumatriptan was more effective than placebo for pain relief (moderate strength of evidence), and more effective than placebo for headache recurrence (low strength of evidence). Results were mixed for pain relief when triptans were compared with other active agents (low strength of evidence). Only one study assessed headache recurrence and found that sumatriptan was significantly less effective than DHE (low strength of evidence). The mixed treatment analysis demonstrated that sumatriptan was similarly effective to orphan drugs and other anti-nauseants, but less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence).

$MgSO_4$ was compared with placebo in three trials and with other active agents in two trials. There was no difference between $MgSO_4$ and placebo for pain relief (low strength of evidence). There was insufficient strength of evidence for headache recurrence. Compared with other active agents, $MgSO_4$ was less effective in reducing pain intensity (moderate strength of evidence).

Antihistamines were compared with placebo in one trial. There was insufficient strength of evidence 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. The mixed treatment analysis demonstrated

that DHE in combination with metoclopramide or neuroleptic agents was one of the more effective treatment options (low strength of evidence).

Table 45. Summary of the strength of evidence for the effectiveness of parenteral interventions versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# studies)	SOE	Summary
Metoclopramide			
Pain intensity–VAS	Metoclopramide vs. placebo (5 RCTs)	Moderate	Significant effect in favor of MET (MD = -21.88; 95% CI: -27.38, -16.38)
	Metoclopramide vs. neuroleptics (4 RCTs)	Low	Not pooled; inconsistent effect across studies
	Metoclopramide vs. other active agents (4 RCTs, 1 NRCT)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Metoclopramide vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.82; 95% CI 0.51, 1.32)
	Metoclopramide vs. neuroleptics (1 RCT)	Insufficient	No significant difference (RR = 0.41; 95% CI: 0.11, 1.51)
	Metoclopramide vs. other active agents (1 RCT)	Insufficient	No significant difference (RR = 0.82; 95% CI: 0.51, 1.33)
Neuroleptics			
Pain intensity–VAS	Neuroleptics vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (MD = -46.59; 95% CI: -54.87, -38.32, I^2 = 46%)
	Neuroleptics vs. other active agents (14 RCTs)	Moderate	Not pooled; statistical and clinical heterogeneity
Pain relief at 1 hr	Neuroleptics vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 3.21; 95% CI: 1.73, 5.95, I^2 = 75%)
Pain free at 1 hr	Neuroleptics vs. placebo (3 RCTs)	Moderate	Significant effect in favor of neuroleptics RR = 4.67; 95% CI: 2.13, 10.24, I^2 = 57%)
Headache recurrence	Neuroleptics vs. placebo (1 RCT)	Low	Significant effect in favor of neuroleptics (RR = 0.28; 95% CI: 0.15, 0.55)
	Neuroleptics vs. other active agents (3 RCTs)	Low	Not pooled; inconsistent effect across studies
NSAIDs			
Pain intensity–VAS	NSAIDs vs. other active agents (5 RCTs)	Low	Not pooled; inconsistent effect across studies
Pain free 1-2 hr	NSAIDs vs. placebo (2 RCTs)	Moderate	Significant effect in favor of NSAIDs (RR = 2.74; 95% CI: 1.26, 5.98)
	NSAIDs vs. other active agents (3 RCTs)	Low	Not pooled; inconsistent effect across studies
Pain response	NSAIDs vs. other active agents (4 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	NSAIDs vs. placebo (1 RCT)	Low	Significant effect in favor of NSAIDs (RR = 0.32; 95% CI: 0.17, 0.62)
	NSAIDs vs. other active agents (1 RCT)	Insufficient	No significant difference (RR = 1.5; 95% CI 0.28, 8.04)
Opioids			
Pain intensity–VAS	Opioids vs. placebo (3 RCTs)	Moderate	Significant effect in favor of opioids (MD = -16.73; 95% CI: -24.12, -9.33)
Pain intensity–VAS	Opioids vs. other active agents (10 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Opioids vs. other active agents (1RCT)	Insufficient	No significant difference (RR = 1.50; 95% CI: 0.28, 8.04)
DHE			
Pain intensity-	DHE vs. other active	Low	Not pooled; inconsistent effect across

VAS	agents (2 RCTs)		studies
Pain relief at 2 hrs	DHE vs. other active agents (1 RCT)	Low	Significant effect favoring sumatriptan (RR = 0.86; 95% CI: 0.76,0.96)
Pain response	DHE vs. active agents (1RCT)	Low	Significant effect favoring NSAIDs (RR = 1.92; 95% CI: 1.10,3.36)
Headache recurrence	DHE vs. active agent (1 RCT)	Low	Significant effect favoring DHE (RR = 0.39; 95% CI: 0.26,0.59)
Triptans			
Headache relief at 60 min	Sumatriptan vs. placebo (3 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 3.06; 95% CI: 2.57, 3.65)
	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.47; 95% CI: 0.90, 2.38)
Pain free status	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 4.61; 95% CI: 3.62, 5.87)
	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.63; 95% CI: 0.85, 3.11)
Headache relief at 120 min	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 2.61; 95% CI: 2.09, 3.26)
	Almotriptan vs. placebo (1 RCT)	Low	Significant effect in favor of almotriptan (RR = 1.65; 95% CI: 1.15, 2.36)
Pain intensity	Sumatriptan vs. active agents (4 RCTs)	Low	Not pooled; inconsistent effect across studies
Headache recurrence	Sumatriptan vs. placebo (4 RCTs)	Low	Significant effect in favor of sumatriptan (RR = 0.72; 95% CI: 0.57, 0.90)
	Sumatriptan vs. active agents (1 RCT)	Low	Significant effect in favor of DHE (RR = 0.39; 95% CI: 0.26, 0.59)
$MgSO_4$			
Pain intensity–VAS	$MgSO_4$ vs. placebo (2 RCTs)	Low	Not pooled; inconsistent effect across studies
	$MgSO_4$ vs. active agents (2 RCTs)	Moderate	Not pooled; results are consistent in favor of active agents
Pain reduction	$MgSO_4$ vs. placebo (2 RCTs)	Low	Not pooled; inconsistent effect across studies.
Headache recurrence	$MgSO_4$ vs. placebo (1 RCT)	Insufficient	No significant effect (RR = 1.01; 95% CI: 0.66,1.54)
Antihistamines			
Pain intensity–VAS	Antihistamine vs. placebo (1 RCT)	Insufficient	No significant effect (MD = 10.40; 95% CI: -7.38, 28.18)
Combination therapy			
Pain intensity–VAS	DHE + MET or DHE + neuroleptics vs. placebo (3 RCTs)	Low	Significant effect in favor of combination therapy (MD = -41.3; 95% CI: -60.9, -22.1)

CI = confidence interval; MET = metoclopramide; MD = mean difference; $MgSO_4$ = magnesium sulphate; RCT = randomized controlled trial; RR = risk ratio; SOE = Summary of Evidence; VAS = Visual Analogue Scale

Key Question 2: Corticosteroids in the prevention of migraine relapse

Seven studies assessed the effectiveness of dexamethasone compared with placebo in the prevention of migraine relapse. 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 strength of evidence; Table 46). Systemic corticosteroids may not be indicated for all headache patients or all headaches; the evidence regarding the response based on subgroups is discussed under Key Question 5 and 6 below.

Table 46. Summary of the strength of evidence for corticosteroids in the prevention of migraine relapse (Key Question 2)

Outcome	Comparison (# studies)	SOE	Summary
Headache recurrence (24–72 hr)	Corticosteroids vs. placebo (7 RCTs)	Moderate	Significant in favor of corticosteroids (RR = 0.68, 95% CI: 0.49, 0.96, I^2 = 63%)
Headache recurrence (7 days)	Corticosteroids vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.70; 95% CI: 0.43, 1.14)
Headache recurrence (30 days)	Corticosteroids vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.90; 95% CI: 0.58, 1.41)

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

Key Question 3: Safety of parenteral interventions versus placebo or an active treatment

We did not conduct a traditional pair-wise meta-analysis of adverse effects because we did not have multiple studies with the same comparisons reporting common adverse effects. However, the summary of adverse effects that we present provides an overall picture of which interventions had high rates of specific adverse effects. This provides a comprehensive summary of adverse effects across studies and interventions for this patient population.

The main side effect of neuroleptic agents was akathisia; the odds of experiencing akathisia was in the range of 10 times greater than with placebo and was similar to metoclopramide. There were few short-term side effects 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/vomiting (11 percent), and chest symptoms (9 percent). There were few short-term side effects reported for opioids. While the risk of dependence and relapse are important long-term side effects, long-term outcomes 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 in 39 percent of the patients; however, this is not surprising since these agents were all delivered subcutaneously. Chest symptoms (5 percent) were relatively infrequent. In patients receiving $MgSO_4$, high rates of skin flushing (10 percent) and local reactions (43 percent) were reported.

Key Question 4: Akathisia

Akathisia is a perplexing 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, as well as provider anxiety. The mixed treatment analysis clearly indicates that metoclopramide and neuroleptics (e.g., prochlorperazine) are the main anti-migraine agents causing these symptoms; however, there is no statistically significant difference in the risk of akathisia between neuroleptics and metoclopramide. Moreover, given the difficulty with the diagnosis of akathisia, it is not surprising that several other agents cause similar symptoms.

Given the concern regarding akathisia symptoms, efforts to prevent these symptoms have been implemented. For example, it is common practice to co-administer antihistamines (e.g., diphenhydramine, hydroxyzine) or anticholinergic agents (e.g., promethazine) with neuroleptics and metoclopramide. This review failed to identify clear evidence for or against the use of these

agents with neuroleptics or metoclopramide to prevent the development of akathisia symptoms (Table 47). The small number of studies and small sample sizes of the included studies produced imprecise point estimates – equivalence cannot be claimed.

Table 47. Summary of strength of evidence for the development of akathisia when anticholinergic agents are added to metoclopramide or phenothiazines

Outcome	Comparison (# studies)	SOE	Summary
Akathisia	Metoclopramide+anticholinergic vs. Phenothiazine+ anticholinergic (1 RCT)	Insufficient	No significant difference (OR = 1.50; 95% CI: 0.24, 9.52)

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

Key Question 5 and 6: Subpopulations

Overall, the evidence accumulated in this review failed to provide direction regarding the typical subpopulations who may differentially respond to the anti-migraine treatment. This group of studies did not often report subgroups based on sex, race, and duration of headaches. In one study where sex was reported as a subgroup, variation in responses were not identified in relapse.[23]

With respect to corticosteroid treatment for the prevention of relapse, some within- and between-study comparisons were identified to assist clinicians in making decisions. The reason this is important is that despite the effectiveness of this agent, the repeated use of high-dose systemic corticosteroids should not be routinely encouraged. In one trial, dexamethasone was less effective in patients who had more residual pain at discharge (VAS scores > 2), and in three trials dexamethasone was more effective in patients who had more prolonged headaches. In addition, in one other published review,[28] authors found that higher doses (≥ 15 mg) of intravenous dexamethasone were more effective than lower does (< 15 mg). These results were repeated here and, while similar trends were observed, the differences were not statistically significant.

Findings in Relationship to What is Already Known

Clinicians treating acute migraine headaches use a wide variety of parenteral agents.[112] Most of the research on practice patterns in migraine therapy that has been conducted in adult patients with acute migraine headaches demonstrates considerable variation as well as the use of non-evidence based treatments.[18] Consequently, this comparative effectiveness review is timely.

This review provides a more comprehensive and up-to-date review of the available evidence than was previously available. This includes evidence from placebo controlled trials and head to head trials. Although there have been individual systematic reviews of DHE,[113] metoclopramide,[114] meperidine,[115] and systemic corticosteroids[28] in the published literature, this review contextualizes each class of medication vis-à-vis every other class of acute migraine therapeutics. To our knowledge, there have been no mixed treatment analyses published regarding this topic. While we did not conduct a meta-analysis of adverse effects, the evidence that we present provides a comprehensive summary of adverse effects across studies and interventions for this patient population. This provides an overall picture of the interventions that had high rates of specific adverse effects.

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 homogenous. Most patients were female aged 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. Consequently, it would appear that these results are generalizable to most ED patients based on sex, race, and age. 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 severe headaches. In other studies, patients rated their headache as severe or moderate. The majority of studies took place in the ED. The results of this review should 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 intravenous agents are being contemplated.

Limitations of the Existing Evidence

The strength of the evidence was low or moderate for the majority of outcomes across the various drug comparisons. These low grades were driven by moderate risk of bias within individual studies and a lack of consistency among studies. Most of the lack of clarity arose from poor descriptions of the system of randomization and describing concealment of allocation; however, this may be a limitation in the reporting and not of the conduct.

There is a relatively small body of evidence for the parenteral treatment of acute migraine headache, and the evidence arises from small studies, usually from single centers. Consequently, unique features (e.g., dose of drug, addition of an anticholinergic) make comparisons difficult. This results in infrequent pooling and unclear direction. The best example of this is the neuroleptic agents where over time the exact agent varied, as did the dose, use of anticholinergic or antihistamine combinations, and other study design issues. 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 the outcomes from the studies included in this review, which hampered efforts to provide meta-graphs 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 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 the ability of the review 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. These observations limited the ability of the review to provide robust estimates of the relative risks associated with the agents. Side effects were examined for individual arms of the trials, and not as comparative effectiveness comparisons.

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 about equivalence. Equivalence claims would require considerably larger sample sizes and 95 confidence intervals that did not include the minimally clinically important differences.

Mixed treatment analyses make an inherent assumption that the direct and indirect evidence estimate the same parameter. In our analyses we observed inconsistency that somewhat belies

this assumption, and may cast some doubt on our results. We also had categories "active combination agents" and "orphan drugs" that do not distinguish between possible heterogeneous treatments within these groups.

In addition to the issues identified above, this comparative effectiveness review has several limitations. Due to the small number of studies for each comparison we were unable to formally assess potential for publication bias. Nonetheless, a comprehensive search of the published and grey 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 on study publications was performed independently using the risk of bias tool, and contact with authors to verify the methods used was not completed. 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:

- Future research 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. Authors may find tools such as the CONSORT statements[116] helpful in designing and reporting on randomized controlled trials.
- 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.
- Since many of the studies 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.
- There are several pressing areas where variation in management may be clarified in the near future, and updating this review should be a priority within 5 years.
- Many trials were small and conducted in a single-center, delaying the dissemination of evidence and knowledge more than necessary. A multi-centered acute migraine headache collaboration or consortium in emergency medicine would be an efficient method to answer the remaining important questions.

- Future trials should investigate important subpopulations who may differentially respond to migraine treatment.
- Few studies reported any information regarding the costs of therapy. Since many of the agents reported in this review have long since been generic and, as a result, are inexpensive, the direct costs of care may not differ. Nonetheless, the variability in adverse effects, relapse, and lost time from life activities suggest that "cost" may be an important consideration to patients and society.
- The results for this review support calls for well powered multi-center studies using standardized methodologies

Conclusions

This report provides the most comprehensive synthesis 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. 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 or DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options. Second, several treatments reported here provide insufficient evidence for continued use. 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, and perhaps cost, 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.

References and Included Studies

1. Goadsby PJ, Lipton RB, Ferrari MD. Migraine--current understanding and treatment. N Engl J Med 2002;346(4):257-70. PMID:11807151

2. Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. Ann Neurol 2004;55(1):19-26. PMID:14705108

3. Link AS, Kuris A, Edvinsson L. Treatment of migraine attacks based on the interaction with the trigemino-cerebrovascular system. J Headache Pain 2008;9(1):5-12. PMID:18217201

4. Jakubowski M, Levy D, Kainz V, et al. Sensitization of central trigeminovascular neurons: blockade by intravenous naproxen infusion. Neuroscience 2007;148(2):573-83. PMID:17651900

5. Jakubowski M, Levy D, Goor-Aryeh I, et al. Terminating migraine with allodynia and ongoing central sensitization using parenteral administration of COX1/COX2 inhibitors. Headache 2005;45(7):850-61. PMID:15985101

6. Diamond S, Bigal ME, Silberstein S, et al. Patterns of diagnosis and acute and preventive treatment for migraine in the United States: results from the American Migraine Prevalence and Prevention study. Headache 2007;47(3):355-63. PMID:17371352

7. Bamford CC, Tepper SJ. Migraine – current understanding and treatment. Techniques Reg Anesth Pain Manage 2009;13(1):20-7.

8. Hu XH, Markson LE, Lipton RB, et al. Burden of migraine in the United States: disability and economic costs. Arch Intern Med 1999;159(8):813-8.

9. Lambert J, Carides GW, Meloche JP, et al. Impact of migraine symptoms on health care use and work loss in Canada in patients randomly assigned in a phase III clinical trial. Can J Clin Pharmacol 2002;9(3):158-64. PMID:12422253

10. Lipton RB, Hamelsky SW, Kolodner KB, et al. Migraine, quality of life, and depression: a population-based case-control study. Neurology 2000;55(5):629-35. PMID:10980724

11. Bigal ME, Kurth T, Santanello N, et al. Migraine and cardiovascular disease: a population-based study. Neurology 2010;74(8):628-35. PMID:20147658

12. Schurks M, Rist PM, Bigal ME, et al. Migraine and cardiovascular disease: systematic review and meta-analysis. BMJ 2009;339:b3914. PMID:19861375

13. Headache Classification Committee of the International Headache Society. Part one- The primary headaches. Cephalalgia 2004;24(Suppl 1):23-136.

14. Friedman BW, Serrano D, Reed M, et al. Use of the emergency department for severe headache. A population-based study. Headache 2009;49(1):21-30. PMID:19040677

15. Goldstein JN, Camargo CA, Jr., Pelletier AJ, et al. Headache in United States emergency departments: demographics, work-up and frequency of pathological diagnoses. Cephalalgia 2006;26(6):684-90. PMID:16686907

16. Friedman BW. Migraine and other primary headache disorders. In: Rowe BH, ed. Evidence-based emergency medicine. 1st ed. Whiley-Blackwell; 2009:493-502.

17. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med 2002;39(3):215-22. PMID:11867972

18. Colman I, Rothney A, Wright SC, et al. Use of narcotic analgesics in the emergency department treatment of migraine headache. Neurology 2004;62(10):1695-700. PMID:15159464

19. Richer LP, Laycock K, Millar K, et al. Treatment of children with migraine in emergency departments: national practice variation study. Pediatrics 2010;126(1):e150-e155. PMID:20530076

20. Richer L, Graham L, Klassen T, et al. Emergency department management of acute migraine in children in Canada: a practice variation study. Headache 2007;47(5):703-10. PMID:17501852

21. Innes GD, Macphail I, Dillon EC, et al. Dexamethasone prevents relapse after emergency department treatment of acute migraine: a randomized clinical trial. CJEM 1999;1(1):26-33. PMID:17659098

22. Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. Neurology 2007;69(22):2038-44. PMID:17942818

23. Rowe BH, Colman I, Edmonds ML, et al. Randomized controlled trial of intravenous dexamethasone to prevent relapse in acute migraine headache. Headache 2008;48(3):333-40. PMID:18047499

24. Burnstein R, Levy D, Jakubowski M. Effects of sensitization of trigeminovascular neurons to triptan therapy during migraine. Rev Neurol (Paris) 2005;161(6-7):658-60. PMID:16141951

25. Dodick D, Lipton RB, Martin V, et al. Consensus statement: cardiovascular safety profile of triptans (5-HT agonists) in the acute treatment of migraine. Headache 2004;44(5):414-25. PMID:15147249

26. Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study.[Erratum appears in Ann Emerg Med 1995 Jun;25(6):857]. Ann Emerg Med 1995;25(4):464-9. PMID:7710149

27. Kelly AM, Kerr D, Clooney M. Impact of oral dexamethasone versus placebo after ED treatment of migraine with phenothiazines on the rate of recurrent headache: a randomised controlled trial. Emerg Med J 2008;25(1):26-9. PMID:18156535

28. Colman I, Freidman BW, Brown MD, et al. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence. BMJ 2008;336(7657):1359-61. PMID:18541610

29. Vinson DR, Drotts DL. Diphenhydramine for the prevention of akathisia induced by prochlorperazine: a randomized, controlled trial. Ann Emerg Med 2001;37(2):125-31. PMID:11174228

30. Higgins JPT ADSJeobotCSMGatCBMG. Chapter 8: Assessing risk of bias in included studies. Cochrane handbook for systematic reviews of interventions Version 5 1 0 [updated March 2011]. 2011. Available from: URL: http://www.cochrane-handbook.org.

31. Follmann D, Elliot P, Suh I. Variance imputation for overviews of clinical trials with continous response. J Clin Epidemiol 1992;45(7):769-73. PMID:1619456

32. Kelly AM, Ardagh M, Curry C, et al. Intravenous chlorpromazine versus intramuscular sumatriptan for acute migraine. Journal of Accident & Emergency Medicine 1997;14(4):209-11. PMID:9248904

33. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments: combining direct and indirect evidence. BMJ 2005;331(7521):897-900. PMID:16223826

34. Lu G, Ades AE. Combination of direct and indirect evidence in mixed treatment comparisons. Stat Med 2004;23(20):3105-24. PMID:15449338

35. Higgins JP, Whitehead A. Borrowing strength from external trials in a meta-analysis. Stat Med 1996;15(24):2733-49. PMID:8981683

36. Smith TC, Spiegelhalter DJ, Thomas A. Bayesian approaches to random-effects meta-analysis: a comparative study. Stat Med 1995;14(24):2685-99. PMID:8619108

37. Dias S, Welton NJ, Caldwell DM, et al. Checking consistency in mixed treatment comparison meta-analysis. Stat Med 2010;29(7-8):932-44. PMID:20213715

38. Gartlehner G, Hansen R, Nissman D. A simple and valid tool distinguished efficacy from effectiveness studies. J Clin Epidemiol 2006;59(10):1040-8. PMID:16980143

39. Owens D, Lohr K, Atkins D. Grading the strength of a body of evidence when comparing medical interventions: Agency for Healthcare Research and Quality and the Effective Health Care Program; AHRQ series paper 5. J Clin Epidemiol 2010;63(5):513-23. PMID:19595577

40. Lee JS, Hobden E, Stiell IG, et al. Clinically important change in the visual analog scale after adequate pain control. Acad Emerg Med 2003;10(10):1128-30.

41. Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. Acad Emerg Med 1996;3(2):142-6.

42. Kelly AM. Does the clinically significant difference in visual analog scale pain scores vary with gender, age, or cause of pain? Acad Emerg Med 1998;5(11):1086-90.

43. Gallagher EJ, Liebman M, Bijur PE. Prospective validation of clinically important changes in pain severity measured on a visual analog scale. Ann Emerg Med 2001;38(6):633-8.

44. Gallagher EJ, Bijur PE, Latimer C, et al. Reliability and validity of a visual analog scale for acute abdominal pain in the ED. Am J Emerg Med 2002;20(4):287-90.

45. Bijur PE, Latimer CT, Gallagher EJ. Validation of a verbally administered numerical rating scale of acute pain for use in the emergency department. Acad Emerg Med 2003;10(4):390-2.

46. Marinsek M, Kovacic D, Versnik D, et al. Analgesic treatment and predictors of satisfaction with analgesia in patients with acute undifferentiated abdominal pain. Eur J Pain 2007;11(7):773-8.

47. Leinisch E, Evers S, Kaempfe N, et al. Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: a double-blind, placebo-controlled parallel group multicenter study. Pain 2005;117(3):396-400. PMID:16153780

48. Carleton SC, Shesser RF, Pietrzak MP, et al. Double-blind, multicenter trial to compare the efficacy of intramuscular dihydroergotamine plus hydroxyzine versus intramuscular meperidine plus hydroxyzine for the emergency department treatment of acute migraine headache. Ann Emerg Med 1998;32(2):129-38. PMID:9701293

49. Shrestha M, Singh R, Moreden J, et al. Ketorolac vs chlorpromazine in the treatment of acute migraine without aura. A prospective, randomized, double-blind trial. Arch Intern Med 1996;156(15):1725-8. PMID:8694672

50. Davis CP, Torre PR, Williams C, et al. Ketorolac versus meperidine-plus-promethazine treatment of migraine headache: evaluations by patients. Am J Emerg Med 1995;13(2):146-50. PMID:7893296

51. Limmroth V, May A, Diener H-C. Lysine-acetylsalicylic acid in acute migraine attacks. European Neurology 1999;41(2):88-93. PMID:10023111

52. Wendt J, Cady R, Singer R, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. Clin Ther 2006;28(4):517-26. PMID:16750463

53. Mushet GR, Cady RK, Baker CC, et al. Efficacy and tolerability of subcutaneous sumatriptan administered using the IMITREX^{R} STATdose^{TM} system. Clin Ther 1996;18(4):687-99. PMID:8879897

54. Thomson AN, Arthur GP, Bergin PS, et al. Subcutaneous sumatriptan in acute treatment of migraine - a multicenter New-Zealand trial. N Z Med J 1993;106(955):171-3. PMID:8389026

55. Cady RK, Wendt JK, Kirchner JR, et al. Treatment of acute migraine with subcutaneous sumatriptan. JAMA 1991;265(21):2831-5. PMID:1851894

56. Winner P, Ricalde O, Le FB, et al. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. Arch Neurol 1996;53(2):180-4. PMID:8639069

57. Cabarrocas X. Efficacy and tolerability of subcutaneous almotriptan for the treatment of acute migraine: a randomized, double-blind, parallel-group, dose-finding study. Clin Ther 2001;23(11):1867-75. PMID:11768838

58. Kostic MA, Gutierrez FJ, Rieg TS, et al. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. Ann Emerg Med 2010;56(1):1-6. PMID:20045576

59. Cameron JD, Lane PL, Speechley M. Intravenous chlorpromazine vs intravenous metoclopramide in acute migraine headache. Acad Emerg Med 1995;2(7):597-602. PMID:8521205

60. Stiell IG, Dufour DG, Moher D, et al. Methotrimeprazine versus meperidine and dimenhydrinate in the treatment of severe migraine: a randomized, controlled trial. Ann Emerg Med 1991;20(11):1201-5. PMID:1952306

61. Lane PL, McLellan BA, Baggoley CJ. Comparative efficacy of chlorpromazine and meperidine with dimenhydrinate in migraine headache. Ann Emerg Med 1989;18(4):360-5. PMID:2705667

62. Jones J, Sklar D, Dougherty J, et al. Randomized double-blind trial of intravenous prochlorperazine for the treatment of acute headache. JAMA 1989;261(8):1174-6. PMID:2915441

63. Tanen DA, Miller S, French T, et al. Intravenous sodium valproate versus prochlorperazine for the

emergency department treatment of acute migraine headaches: a prospective, randomized, double-blind trial. Ann Emerg Med 2003;41(6):847-53. PMID:12764341

64. Weaver CS, Jones JB, Chisholm CD, et al. Droperidol vs prochlorperazine for the treatment of acute headache. J Emerg Med 2004;26(2):145-50. PMID:14980334

65. Seim MB, March JA, Dunn KA. Intravenous ketorolac vs intravenous prochlorperazine for the treatment of migraine headaches. Acad Emerg Med 1998;5(6):573-6. PMID:9660282

66. Demirkaya S, Vural O, Dora B, et al. Efficacy of intravenous magnesium sulfate in the treatment of acute migraine attacks. Headache 2001;41(2):171-7. PMID:11251702

67. Miller MA, Levsky ME, Enslow W, et al. Randomized evaluation of octreotide vs prochlorperazine for ED treatment of migraine headache. Am J Emerg Med 2009;27(2):160-4. PMID:19371522

68. Hill CH, Miner JR, Martel ML. Olanzapine versus droperidol for the treatment of primary headache in the emergency department. Acad Emerg Med 2008;15(9):806-11. PMID:19244630

69. Callan JE, Kostic MA, Bachrach EA, et al. Prochlorperazine vs. promethazine for headache treatment in the emergency department: a randomized controlled trial. J Emerg Med 2008;35(3):247-53. PMID:18534808

70. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. Ann Emerg Med 2008;52(4):399-406. PMID:18006188

71. Donaldson D, Sundermann R, Jackson R, et al. Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: a multicenter, double-blinded, placebo-controlled randomized clinical trial. Am J Emerg Med 2008;26(2):124-30. PMID:18272089

72. Alemdar M, Pekdemir M, Selekler HM. Single-dose intravenous tramadol for acute migraine pain in adults: a single-blind, prospective, randomized, placebo-controlled clinical trial. Clin Ther 2007;29(7):1441-7. PMID:17825695

73. Baden EY, Hunter CJ. Intravenous dexamethasone to prevent the recurrence of benign headache after discharge from the emergency department: a randomized, double-blind, placebo-controlled clinical trial. CJEM 2006;8(6):393-400. PMID:17209488

74. Friedman BW, Hochberg M, Esses D, et al. A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines. Headache 2006;46(6):934-41. PMID:16732839

75. Honkaniemi J, Liimatainen S, Rainesalo S, et al. Haloperidol in the acute treatment of migraine: a randomized, double-blind, placebo-controlled study. Headache 2006;46(5):781-7. PMID:16643581

76. Engindeniz Z, Demircan C, Karli N, et al. Intramuscular tramadol vs. diclofenac sodium for the treatment of acute migraine attacks in emergency department: a prospective, randomised, double-blind study. Journal of Headache and Pain 2005;6(3):143-8. PMID:16355295

77. Friedman BW, Corbo J, Lipton RB, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. Neurology 2005;64(3):463-8. PMID:15699376

78. Cete Y, Dora B, Ertan C, et al. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the Emergency Department. Cephalalgia 2005;25(3):199-204. PMID:15689195

79. Meredith JT, Wait S, Brewer KL. A prospective double-blind study of nasal sumatriptan versus IV ketorolac in migraine. Am J Emerg Med 2003;21(3):173-5. PMID:12811706

80. Richman PB, Allegra J, Eskin B, et al. A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. Am J Emerg Med 2002;20(1):39-42. PMID:11781912

81. Corbo J, Esses D, Bijur PE, et al. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. Ann Emerg Med 2001;38(6):621-7. PMID:11719739

82. Miner JR, Fish SJ, Smith SW, et al. Droperidol vs. prochlorperazine for benign headaches in the emergency department. Acad Emerg Med 2001;8(9):873-9. PMID:11535479

83. Blanda M, Rench T, Gerson LW, et al. Intranasal lidocaine for the treatment of migraine headache: a randomized, controlled trial. Acad Emerg Med 2001;8(4):337-42. PMID:11282668

84. Ginder S, Oatman B, Pollack M. A prospective study of IV magnesium and IV prochlorperazine in the treatment of headaches. J Emerg Med 2000;18(3):311-5. PMID:10729668

85. Drotts DL, Vinson DR. Prochlorperazine induces akathisia in emergency patients. Ann Emerg Med 1999;34(4:Pt 1):t-75. PMID:10499947

86. Jones J, Pack S, Chun E. Intramuscular prochlorperazine versus metoclopramide as single-agent therapy for the treatment of acute migraine headache. Am J Emerg Med 1996;14(3):262-4. PMID:8639197

87. Coppola M, Yealy DM, Leibold RA. Randomized, placebo-controlled evaluation of prochlorperazine versus metoclopramide for emergency department treatment of migraine headache. Ann Emerg Med 1995;26(5):541-6. PMID:7486359

88. Jovicic A, Maric D, Ilic T. Treatment of acute migraine attacks [Serbian]. Vojnosanitetski Pregled 1995;52(1):44-8. PMID:7638950

89. Duarte C, Dunaway F, Turner L, et al. Ketorolac versus meperidine and hydroxyzine in the treatment of acute migraine headache: a randomized, prospective, double-blind trial. Ann Emerg Med 1992;21(9):1116-21. PMID:1514724

90. Tek DS, McClellan DS, Olshaker JS, et al. A prospective, double-blind study of metoclopramide hydrochloride for the control of migraine in the emergency department. Ann Emerg Med 1990;19(10):1083-7. PMID:2221512

91. Bell R, Montoya D, Shuaib A, et al. A comparative trial of three agents in the treatment of acute migraine headache. Ann Emerg Med 1990;19(10):1079-82. PMID:2221511

92. McEwen JI, O'Connor HM, Dinsdale HB. Treatment of migraine with intramuscular chlorpromazine. Ann Emerg Med 1987;16(7):758-63. PMID:3592329

93. Tek D, Mellon M. The effectiveness of nalbuphine and hydroxyzine for the emergency treatment of severe headache. Ann Emerg Med 1987;16(3):308-13. PMID:3544982

94. Frank LR, Olson CM, Shuler KB, et al. Intravenous magnesium for acute benign headache in the emergency department: A randomized double-blind placebo-controlled trial. CJEM 2004;6(5):327-32. PMID:17381989

95. Krymchantowski AV, Silva MTT. Intravenous lysine clonixinate for the acute treatment of severe migraine attacks: a double-blind, randomized, placebo-controlled study. Current Therapeutic Research - Clinical and Experimental 2003;64(8):505-13.

96. Bigal ME, Bordini CA, Speciali JG. Intramuscular diclofenac in the acute treatment of migraine: A double-blind placebo controlled study. [Portuguese]. Arq Neuropsiquiatr 2002;60(2 B):410-5. PMID:12131942

97. Larkin GL, Prescott JE. A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. Ann Emerg Med 1992;21(8):919-24. PMID:1497157

98. Klapper JA, Stanton JS. Ketorolac versus DHE and metoclopramide in the treatment of migraine headaches. Headache 1991;31(8):523-4. PMID:1960056

99. Fiesseler FW, Shih R, Szucs P, et al. Steroids for migraine headaches: a randomized double-blind, two-armed, placebo-controlled trial. J Emerg Med 2011;40(4):463-8. PMID:19846269

100. Edwards KR, Norton J, Behnke M. Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache. Headache 2001;41(10):976-80. PMID:11903525

101. Aktas C, Giray S, Sarikaya S, et al. Ondansetron: an agent to be included in the emergency treatment of migraine headache? Healthmed 2011;5(1):187-93.

102. Bigal ME, Bordini CA, Speciali JG. Intravenous Chlorpromazine in the Emergency Department treatment of migraines: A randomized controlled trial. J Emerg Med 2002;23(2):141-8. PMID:12359281

103. Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: a multicenter study.[Erratum appears in Ann Emerg Med 1995 Jun;25(6):857]. Ann Emerg Med 1995;25(4):464-9. PMID:7710149

104. Klapper J, Stanton J. The emergency treatment of acute migraine headache - a comparison of intravenous dihydroergotamine, dexamethasone, and placebo. Cephalalgia 1989;11:159-60.

105. Callaham M, Raskin N. A controlled study of dihydroergotamine in the treatment of acute migraine headache. Headache 1986;26(4):168-71. PMID:3519528

106. Jones J, Brown MD, Bermingham M, Anderson I, Perrin J. 2003: SAEM Annual Meeting Abstracts. Efficacy of parenteral dexamethasone to prevent relapse after emergency department treatment of acute migraine. Academic Emergency Medicine 10[5], 423-576. 2003.

107. Belgrade MJ, Ling LJ, Schleevogt MB, et al. Comparison of single-dose meperidine, butorphanol, and dihydroergotamine in the treatment of vascular headache. Neurology 1989;39(4):590-2. PMID:2648190

108. Karachalios GN, Fotiadou A, Chrisikos N, et al. Treatment of acute migraine attack with diclofenac sodium: a double-blind study. Headache 1992;32(2):98-100. PMID:1551795

109. Hoag R, Mortimer L. Methotrimeprazine compared to meperidine and dimenhydrinate in the treatment of migraine headache. CAEP Review 1986;May:29-31.

110. Cicek M, Karcioglu O, Parlak I, et al. Prospective, randomised, double blind, controlled comparison of metoclopramide and pethidine in the emergency treatment of acute primary vascular and tension type headache episodes. Emerg Med J 2004;21(3):323-6. PMID:15107371

111. Monzillo PH, Nemoto PH, Costa AR, et al. Acute treatment of migraine in emergency room: comparative study between dexametasone and haloperidol. Preliminary results [Portuguese]. Arq Neuropsiquiatr 2004;62(2B):513-8. PMID:15273854

112. Vinson DR, Hurtado TR, Vandenberg JT, et al. Variations among emergency departments in the treatment of benign headache. Ann Emerg Med 2003;41(1):90-7. PMID:12514688

113. Colman I, Brown MD, Innes GD, et al. Parenteral dihydroergotamine for acute migraine headache: A systematic review of the literature. Ann Emerg Med 2005;45(4):393-401. PMID:15795718

114. Colman I, Brown MD, Innes GD, et al. Parenteral metoclopramide for acute migraine: meta-analysis of randomised controlled trials. BMJ 2004;329(7479):1369-73. PMID:15550401

115. Friedman BW, Kapoor A, Friedman MS, et al. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled trials. Ann Emerg Med 2008;52(6):705-13. PMID:18632186

116. Moher D, Hopewell S, Schulz KF, et al. CONSORT 2010 Explanation and Elaboration: Updated guidelines for reporting parallel group randomised trials. J Clin Epidemiol 2010;63(8):e1-37. PMID:20346624

Acronyms

AHRQ	Agency for Healthcare Research and Quality
CER	Comparative Effectiveness Review
CI	confidence interval
DHE	dihydroergotamine
ED	emergency department
EPC	Evidence-based Practice Center
FDA	Food and Drug Administration
GRADE	Grading of Recommendations Assessment,Development and Evaluation
HT	5-hydroxytryptamine
IQR	interquartile range
IV	intravenous
kg	kilogram(s)
MD	mean difference
mg	milligram(s)
$MgSO_4$	magnesium sulphate
ml	milliliter(s)
mm	millimeter(s)
NRCT	nonrandomized controlled trial
NSAIDs	nonsteroidal anti-inflammatory drug
OR	odds ratio
RCT	randomized controlled trial
RR	relative risk
VAS	Visual Analogue Scale