Effective Health Care Program

Comparative Effectiveness Review
Number 84

Acute Migraine Treatment in Emergency Settings

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The information in this report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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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 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 are essential to the Effective Health Care Program. Please visit the Web site (www.effectivehealthcare.ahrq.gov) to see draft research questions and reports or to join an email 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 email to epc@ahrq.hhs.gov.

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Acute Migraine Treatment in Emergency Settings

Structured Abstract

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

Data sources. In consultation with a librarian, we searched 10 electronic databases, conference proceedings, clinical trials registers, and reference lists.

Methods. Two reviewers independently selected studies, assessed risk of bias, extracted data, and graded the strength of evidence (SOE). 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 71 controlled trials. Risk of bias was low for 28 percent of the trials, unclear for 61 percent, and high for 11 percent. Overall, active interventions were more effective than placebo for pain relief and headache recurrence. Most head-to-head comparisons for pain reduction were based on single trials resulting in insufficient SOE. The mixed-treatment analysis showed that the most effective treatments were combination therapy (i.e., dihydroergotamine [DHE] added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low SOE), with a pain reduction of approximately 40 mm on a visual analog scale (VAS). Metoclopramide monotherapy, opioids, and nonsteroidal anti-inflammatories (NSAIDs) were the next most effective treatments, with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective, with a pain reduction of approximately 12-16 mm.

Short-term side effects were infrequent, and considered minor and self-limiting. No two studies reported the same side effects for the same pair of interventions; therefore, the SOE is insufficient to conclude which treatment results in more or fewer adverse effects. Based on the mixed-treatment analysis, the odds of experiencing akathisia symptoms following administration of metoclopramide or neuroleptic agents were 9.4 and 10.7 times greater than with placebo, respectively. The risk of sedation following administration of metoclopramide or neuroleptic agents was 17 percent. The most common short-term side effects for triptans were skin reactions, local reactions, and sedation. For patients receiving DHE, the most common side effects were skin and local reactions, sedation, digestive issues, nausea or vomiting, and chest symptoms. Few side effects were reported for NSAIDS or opioids. In patients receiving magnesium sulfate, high rates of skin flushing and local reactions were reported.

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. Neuroleptic monotherapy and DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options for pain relief (VAS). Systemic corticosteroids effectively prevent headache relapse, especially in patients with prolonged headaches. More research is required to identify the most effective parenteral treatments for adults with acute migraine.

Contents

Tables

Figures

Appendixes

Executive Summary

Introduction

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

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

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

Table A. Summary of pharmacological interventions for acute migraine

Intervention	Generic Name	Trade Name(s)	Mode of Administration
Agents for Procedural Sedation	Ketamine	Ketalar	IV, IM
	Ketofol	NA	IV
	Propofol	Diprivan, Lusedra	IV
	Anticonvulsants		
	Magnesium sulfate	Magnesium sulfate	IV, IM
	Valproic acid	Depacon	IV
Antiemetics	Metoclopramide	Maxeran	IM
		Reglan	IV, IM
	Trimethobenzamide	Tigan, Tebamide	IM
Corticosteroids	Betamethasone	Celestone, Soluspan	IM
	Budesonide	Entocort EC	Oral
	Cortisone	Cortone	Oral, IM
	Dexamethasone	Decadron	IM, IV
	Hydrocortisone	Solu-Cortef	Oral
	Methylprednisolone	Depo-Medrol	IM
		Solu-Medrol	IV, IM
	Prednisolone	Prelone	Oral
	Prednisone	Deltasone	Oral
Ergots	Dihydroergotamine	DHE 45	IV, IM, SC
	NSAIDs		
	Ketorolac	Toradol	IV, IM
Opioids	Butorphanol	Butorphanol tartrate	IV, IM
	Buprenorphine	Buprenex	IM, IV
	Fentanyl	Sublimaze	IM, IV
	Hydromorphone	Dilaudid	SC, IM, IV
	Meperidine (pethidine)	Demerol	IV, IM
	Morphine	Apokyn	SC
		Astramorph PF, DepoDur, Duramorph PF, Infumorph	IV
	Nalbuphine	Nubain	SC, IM, IV
	Tramadol	Conzip, Ryzolt, Ultracet, Ultram, Ralivia, Zytram XL	Oral, IM, IV
Neuroleptics	Chlorpromazine	Largactil	IV, IM
	Droperidol	Inapsine	IV, IM
	Haloperidol	Haldol	IV, IM
	Prochlorperazine	Stemetil, Compazine (other modes available)	IV, IM
Triptan Agents	Sumatriptan	Alsuma, Imitrex (other modes available), Sumavel DosePro	SC
Other Agents	Hydroxyzine	Atarax, Vistaril	Oral, IM
	Lidocaine	Xylocaine	IV, SC
	Promethazine	Phenergan	IV, IM

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

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

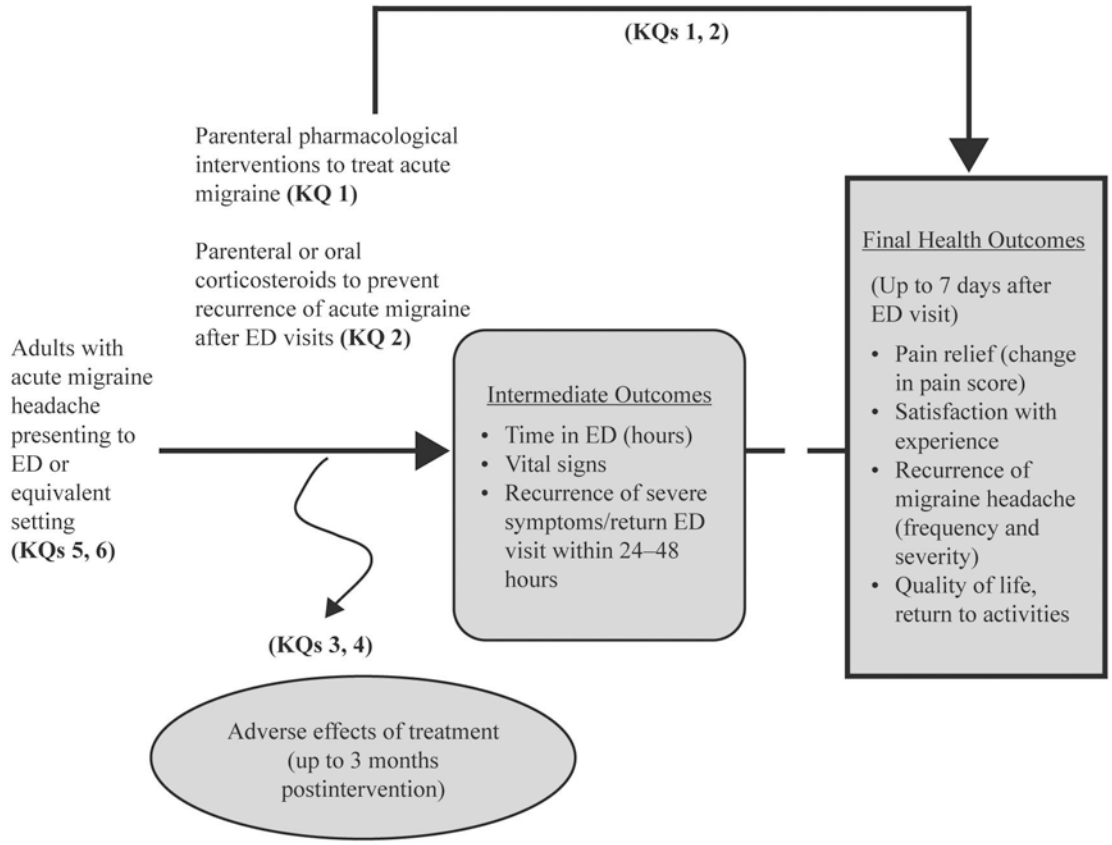
investigate akathisia associated with metoclopramide and phenothiazines. A third focus is to examine the benefit and risk of using corticosteroids for preventing recurrence of acute migraine that results in a return visit to a physician or ED.

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. Do the effectiveness and safety of the parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and nonresponders while in the ED?
6. Do the effectiveness and safety of adding parenteral or oral corticosteroids to acute parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and nonresponders?

Figure A provides an analytic framework to illustrate the population (P), interventions (I), control/comparison (C), and outcomes (O) that guided the literature search and synthesis. This figure depicts the KQs within the context of the PICOTS (population, intervention, comparator, outcomes, timing of outcome measurement, and setting). In general, the figure illustrates a comparison of parenteral pharmacological interventions and parenteral or oral corticosteroid interventions versus standard care, placebo, or an active comparator in terms of intermediate outcomes such as time in ED, recurrence of severe symptoms, or return ED visits within 24 to 48 hours, and final outcomes such as pain relief, satisfaction with experience, quality of life, and return to activities. Adverse effects may occur at any point after the treatment is received and were assessed up to 3 months postintervention.

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

Literature Search Strategy

A research librarian systematically searched the following electronic databases: MEDLINE®, Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effectiveness, International Pharmaceutical

Abstracts, PASCAL, Biosis Previews, Science Citation Index Expanded, and Conference Proceedings Citation Index-Science. Databases were searched from inception to January 5, 2012. The search strategy did not employ any study design search filters, nor were language restrictions applied.

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

Inclusion and Exclusion Criteria

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

Study Selection

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

Data Extraction

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

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

We extracted adverse-effect data as they were reported by the authors of each study. The adverse effects of interest were determined a priori in consultation with the Technical Expert Panel. Due to variable comparisons and reporting, the frequency of adverse effects was examined for individual arms of the trials and not as comparisons of effectiveness. For each adverse effect, the number of patients in each treatment group (e.g., intervention, placebo) and the number of patients with an adverse effect were recorded.

Quality (Risk-of-Bias) Assessment

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

Data Analysis

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

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

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

Applicability

The applicability of the body of evidence was assessed following the PICOTS format used to assess study characteristics.[24] Specific factors that were considered included sex, age, race or

ethnicity, baseline headache severity, clinical setting (e.g., non-ED), and geographic setting (e.g., countries other than in North America).

Grading the Body of Evidence

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

Results

Description of Included Studies

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

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

The studies were published between 1986 and 2011. The majority were conducted in North America (75 percent). Sample sizes varied, with an overall median of 64 patients per study (interquartile range: 40 to 100). For the majority of studies, pain relief or severity was the primary outcome. In 43 studies (61 percent), migraine was classified using criteria established by the International Headache Society.

Methodological Quality of Included Studies

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

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

Key Findings

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

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

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

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

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

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

Opioids were compared with placebo in 3 trials and with other active treatments in 13 trials (Table B). Opioids were more effective than placebo for pain relief (moderate SOE). Results were mixed for opioids compared with other active agents for pain relief. Single trials compared

opioids with other opioids (e.g., nalbuphine, meperidine), hydroxyzine, methotrimeprazine, metoclopramide, neuroleptic agents, NSAIDs, dexamethasone, and DHE (insufficient SOE). The mixed-treatment analysis demonstrated that opioids were similarly effective to NSAIDs and metoclopramide for VAS-rated pain relief (low SOE).There was insufficient SOE for headache recurrence when comparing opioids and other active agents.

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

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

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

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

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

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

Intervention	Outcome	Comparison (# Studies)	SOE	Summary
Metoclopramide	Pain intensity–VAS	Metoclopramide vs. placebo (5 RCTs)	Moderate	Significant effect in favor of metoclopramide (MD = -21.88; 95% CI, -27.38 to -16.38; I^2 = 0%)
	Change in pain–VAS	Metoclopramide vs. neuroleptics (4 RCTs)	Low	Significant effect in favor of neuroleptics (MD = 16.45; 95% CI, 2.08 to 30.83; I^2 = 81%)
	Change in pain–VAS	Metoclopramide vs. prochlorperazine (2 RCTs)	Low	No significant difference between groups (MD = 19.27; 95% CI, -8.85 to 47.38; I^2 = 90%)
Neuroleptics	Pain intensity–VAS	Neuroleptics vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (MD = -46.59; 95% CI, -54.87 to -38.32, I^2 = 46%)
	Headache relief (1 hr)	Neuroleptic vs. placebo (5 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 2.69; 95% CI, 1.66 to 4.34; I^2 = 76%)
	Pain free (1 hr)	Neuroleptic vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 3.38; 95% CI, 1.16 to 9.83; I^2 = 90%)
	Headache recurrence (24 hrs)	Neuroleptic vs. placebo (2 RCTs)	Low	No significant difference between groups (RR = 0.46; 95% CI, 0.19 to 1.10; I^2 = 78%)
	Change in pain–VAS	Metoclopramide vs. prochlorperazine (2 RCTs)	Low	No significant difference between groups (MD = 19.27; 95% CI, -8.85 to 47.38; I^2 = 90%)
	Change in pain–VAS	Prochlorperazine vs. droperidol (2 RCTs)	Low	No significant difference between groups (MD = 9.12; 95% CI, -8.62 to 26.86)
	Headache relief	Prochlorperazine vs. droperidol (2 RCTs)	Moderate	Significant effect in favor of droperidol (RR = 0.81; 95% CI, 0.68 to 0.98)
NSAIDs	Pain free at 1–2 hrs	NSAIDs vs. placebo (2 RCTs)	Moderate	Significant effect in favor of NSAIDs (RR = 2.74; 95% CI, 1.26 to 5.98; I^2 = 47%)
Opioids	Pain intensity–VAS	Opioids vs. placebo (3 RCTs)	Moderate	Significant effect in favor of opioids (MD = -16.73; 95% CI, -24.12 to -9.33; I^2 = 0%)
Triptans	Headache relief at 60 min	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 3.03; 95% CI, 2.59 to 3.54; I^2 = 0%)
	Headache relief at 120 min	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 2.61; 95% CI, 2.09 to 3.26; I^2 = 21%)
	Headache relief at 30 min–VAS	Sumatriptan vs. placebo (2 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = -15.45; 95% CI, -19.49 to -11.41; I^2 = 0%)
	Pain-free status	Sumatriptan vs. placebo (5 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 4.73; 95% CI, 3.77 to 5.94; I^2 = 0%)
	Headache recurrence at 24 hr in the ED	Sumatriptan vs. placebo (4 RCTs)	Low	Significant effect in favor of sumatriptan (RR = 0.72; 95% CI, 0.57 to 0.90; I^2 = 23%)

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

Intervention	Outcome	Comparison (# Studies)	SOE	Summary
$MgSO_4$	Pain intensity–VAS	$MgSO_4$ vs. placebo (3 RCTs)	Moderate	Significant effect in favor of $MgSO_4$ (MD = -9.73; 95% CI, -16.75 to -2.72; I^2 = 0%)
	Headache recurrence	$MgSO_4$ vs. placebo (2 RCTs)	Low	No significant difference between groups (RR = 0.68; 95% CI, 0.29 to 1.63; I^2 = 78%)
Mixed-Treatment Analysis	Pain reduction–VAS	Mixed-treatment comparison (15 RCTs)	Low	Combination therapy: -41.3 mm (95% CI, -60.9 to -22.1) Neuroleptics: -40.3 mm (95% CI, -49.0 to -31.7) NSAIDs: -25.3 mm (95% CI, -38.8 to -12.0) Opioids: -24.8 mm (95% CI, -35.7 to -14.2) Metoclopramide : -23.9 mm (95% CI, -33.3 to -14.5) DHE: -16.3 mm (95% CI, -32.6 to -0.6) Orphan agents: -13.2 mm (95% CI, -23.6 to -2.7) Sumatriptan: -12.3 mm (95% CI, -23.8 to -0.5) Other antinauseants: -9.4 mm (95% CI, -29.2 to 11.1)

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

Key Question 2: Corticosteroids in the Prevention of Migraine Relapse

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

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

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

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

Key Question 3: Adverse Effects

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

General Findings by Intervention Class

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

Vomiting

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

Sedation/Somnolence

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

Dizziness

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

Local Reaction

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

Skin Reactions

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

Extrapyramidal Symptoms

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

Other Adverse Effects

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

Key Question 4: Akathisia

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

We conducted a post hoc mixed-treatment analysis of 15 studies that reported akathisia symptoms as a side effect. The analysis showed that metoclopramide and neuroleptics (e.g., prochlorperazine) are the antimigraine agents most likely to cause these symptoms. The odds of experiencing akathisia symptoms following administration of these drugs were in the range of 10 times as great as the odds with placebo. Although other agents were associated with akathisia in the mixed-treatment analysis, lack of precise diagnostic criteria may limit these results.

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

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

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

Key Questions 5 and 6: Subpopulations

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

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

Summary and Discussion

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

Findings in Relationship to What Is Already Known

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

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

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

Applicability

The study populations included in this review were relatively homogeneous. Most patients were female, and the mean age was generally between 30 and 40 years. Few studies reported on race or ethnicity; however, race was not an inclusion or exclusion criterion for any of the trials. Therefore, it would appear that these results are generalizable to most patients with acute migraine seen in similar EDs based on sex and age. Results may not apply to patients seen in EDs that serve more culturally diverse populations. It is unknown whether males respond differently than females to the interventions included in this review. Similarly, it is unknown whether the results of this review apply to older populations.

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

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

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

Limitations of the Existing Evidence

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

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

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

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

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

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

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

Future Research

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

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

Conclusions

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

with this common disorder. While the evidence collated here is an important step, more research is required in order to identify the most effective and safest parenteral medication for acute migraine.

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Introduction

Background

Condition

Migraine is a chronic neurovascular disorder characterized by dysfunction of central and peripheral nociceptive pathways and intracranial vasculature.[1] Migraine is characterized by a moderate to severe, recurrent, unilateral or bilateral, throbbing headache that can last hours to days. It may be accompanied by nausea, vomiting, and sensitivity to light, sound, touch, and/or smell. Approximately 25 percent of people with migraine experience transient visual disturbance, motor symptoms, or language disturbance.[1,2] The triggers of migraine headaches are multi-factorial, and the pathophysiology is complex and incompletely understood. Current research suggests that migraines occur as a result of a cascade of events involving activation of the trigeminovasucalar system, cortical spreading depression, and neuronal sensitization.[3] Ongoing research in migraine genetics indicates that there may be a genetic disposition to migraine.[4]

Migraine affects 12 percent of the general population in the United States.[5] 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.[6] In the United States, migraine and related medical issues result in costs of more than $13 billion per year due to lost productivity.[7] In Canada, this annual cost has been estimated at $3,025 per patient due to medical and indirect costs.[8]

Migraine has a negative impact on overall quality of life.[9] It is associated with psychiatric and medical comorbidities including major depressive disorder, bipolar disorder, anxiety and social phobias, cardiovascular risk,[10] and stroke.[11] 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.[5]

Diagnosis and Treatment

Migraine Headaches

Headaches 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.[2] Migraines come in several types; some are more common than others. A migraine headache preceded by an aura (e.g., a set of self-limited sensory [visual, tactile, and/or olfactory] symptoms) is referred to as a ***classic*** migraine. Headaches not preceded by an aura are referred to as ***common*** migraines. 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

In contrast, chronic migraine is a specific type of migraine headache; it is defined as headache on >15 days per month for at least 3 months.[2]

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.[12] In the United States, headaches accounted for 2.2 percent of visits or 2.1 million ED visits per year.[13] Of patients who use an ED for treatment of migraine, 19 percent make multiple visits over the course of 1 year.[14]

While headache is a common cause of presentation to the ED, there is substantial practice variability among emergency clinicians in North America.[15-18] Twenty disparate parenteral agents are used to treat acute migraine in EDs in the United States.[15] 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.[17] Moreover, over-use of opioids has been observed in several studies.[15,16] 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 (IV) nonsteroidal anti-inflammatory agents (NSAIDs), and opioids. While earlier studies have shown that opioids are commonly used,[15,16] the most common first line agents used for migraine treatment in more recent studies include metoclopramide and prochlorperazine, which is a phenothiazine.[19-21] While alternative phenothiazines exist, prochlorperazine is usually preferred due to its efficacy and safety.[22,23] IV DHE and ketorolac are also used to treat acute migraine. Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and their association with a higher risk of headache relapse.[14] 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).[21] Table 1 summarizes pharmacological interventions that have been approved by the U.S. Food and Drug Administration and that are used, often off-label, for acute migraine.

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

Side Effects

The second objective of this CER was 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 examined 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 was to examine the benefit and risk of using corticosteroids for preventing recurrence of acute migraine.

Table 1. Summary of pharmacological interventions for acute migraine

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

Table 1. Summary of pharmacological interventions for acute migraine (continued)

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

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

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 rationale for focusing on parenteral interventions is threefold: (1) the majority of patients presenting to the ED have already failed oral medications and other home remedies; (2) most patients presenting to the ED are experiencing nausea and/or vomiting so continued oral interventions can prove to be futile; (3) the rapid onset and efficacy of parenteral agents is appealing to both patients and clinicians. 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:

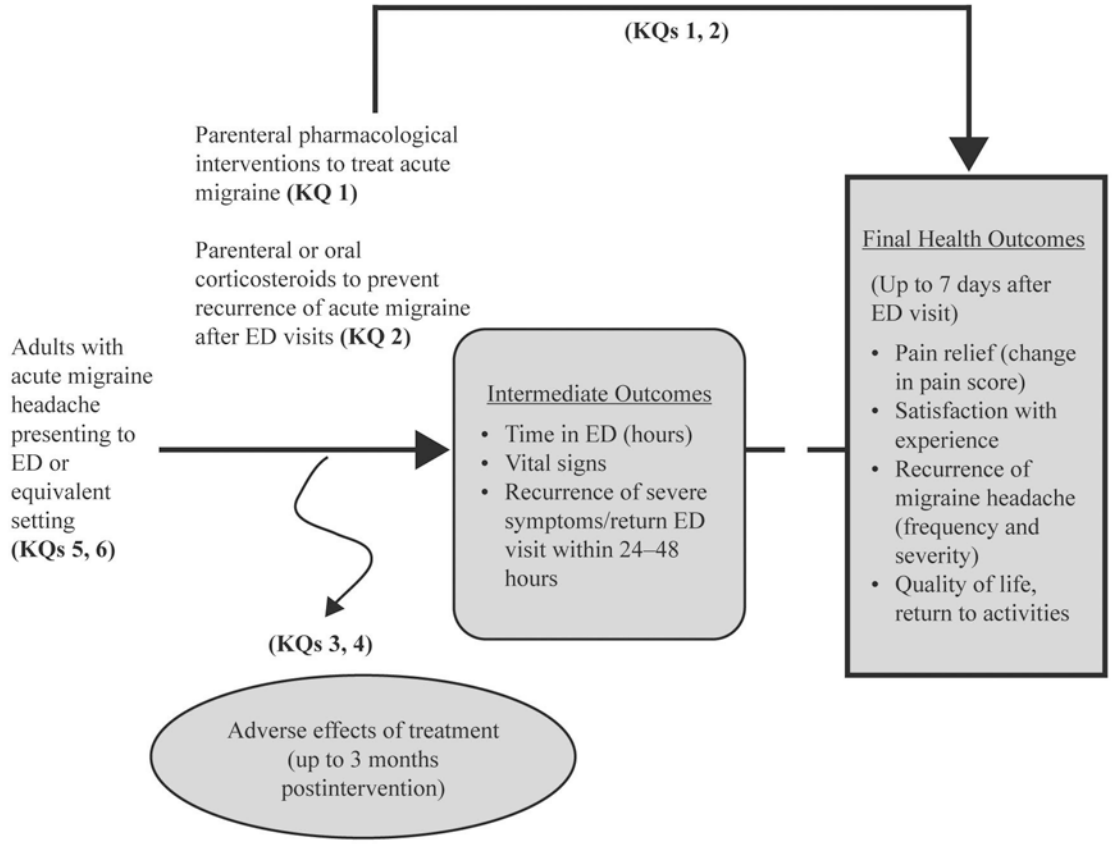
Does the effectiveness and safety of the parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and non-responders while in the ED?

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 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 University of Alberta Evidence-based Practice Center (EPC) was commissioned to conduct a preliminary literature review to gauge the availability of evidence and to draft key research questions for a CER. Investigators from the EPC developed the Key Questions (KQs) in consultation with the Agency for Healthcare Research and Quality (AHRQ) EPC Program, the Scientific Resource Center, and a panel of key informants. AHRQ posted the KQs on their 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 January 5, 2012. 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 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. Equivalent settings included headache or pain clinics, neurology departments, physician offices and public health centers. 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).

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 included 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 above parenteral interventions)
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

Table 2. Eligibility criteria for this review (continued)

Category	Criteria
Outcomes of interest	Pain relief/change in pain score (measured either as a visual analogue score, a Likert scale of pain, or a 10-point verbal scale) Complete elimination of pain prior to ED discharge Vital signs (i.e., blood pressure, pulse) Time in the ED (in minutes of total time and post-ED physician time). Recurrence of headache (headache relieved in the ED and recurring within the followup period) Health services utilization (e.g., return visit to ED defined as an unscheduled visit for worsening symptoms) Patient satisfaction with experience Quality of life/return to activities Adverse effects of intervention(s): Sedation/somnolence Dizziness Restless legs/akathisia Anxiety Vomiting Chest symptoms, palpitations Skin flushing Other side effects There was no minimum followup duration requirement for inclusion.

ED = emergency department; $MgSO_4$ = magnesium sulfate; NRCT = nonrandomized controlled trial; NSAID = nonsteroidal anti-inflammatory drug; RCT = randomized controlled trial

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 U.S. Food and Drug Administration 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.

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 scale [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.

It is recognized that many drugs have various effects (e.g., a neuroleptic can be used for the antiemetic treatment of nausea and vomiting). In consultation with the technical expert panel, the research team organized drugs by the classes outlined in Table 1. 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 were grouped with the main drug class (e.g., prochlorperazine plus antihistamine versus metoclopramide was included in the neuroleptics versus metoclopramide category).

We extracted drug related adverse effects as they were reported by the authors of each study. The terminology used to describe adverse effect outcomes varied across studies. The adverse effects of interest were determined a priori in consultation with the technical expert panel and were classified as outlined in Table 3. For each adverse effect, the number of patients in each treatment, active comparator, or placebo group, and the number of patients experiencing 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 adverse effects. 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.

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, intravenous 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

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% confidence intervals (CI) were used to calculate approximate standard deviations. We calculated p-values when they were not reported. Change from baseline data were 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 to assess pain. 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 the 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, metoclopramide). 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 that allows us to provide an overall picture of which interventions had a high risk of specific adverse effects. For each adverse effect category, risks (i.e., incidence rates) were pooled using a random effects model to obtain a summary estimate and 95 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.[33]

For two outcomes, pain relief (VAS) 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.[34-36] The studies that were included in these analyses represented similar populations, outcomes, and designs, and the research team judged that clinical heterogeneity was 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 (VAS). 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.[37] 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.[38]

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.[39] 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. Specific factors that were considered included sex, age, race or ethnicity, baseline headache severity, clinical setting (e.g., non-ED), and geographic setting (e.g., countries other than in North America).

Grading the 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[40] and resolved disagreements 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 related outcomes 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, 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 unclear 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.[40] In cases where results were not pooled, the overall strength of evidence rating was not downgraded. We did not make estimates regarding precision when it was inappropriate to pool results from studies. Single trials, particularly those with small sample sizes, were graded as having insufficient strength of evidence despite being precise and having low risk of bias.

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.

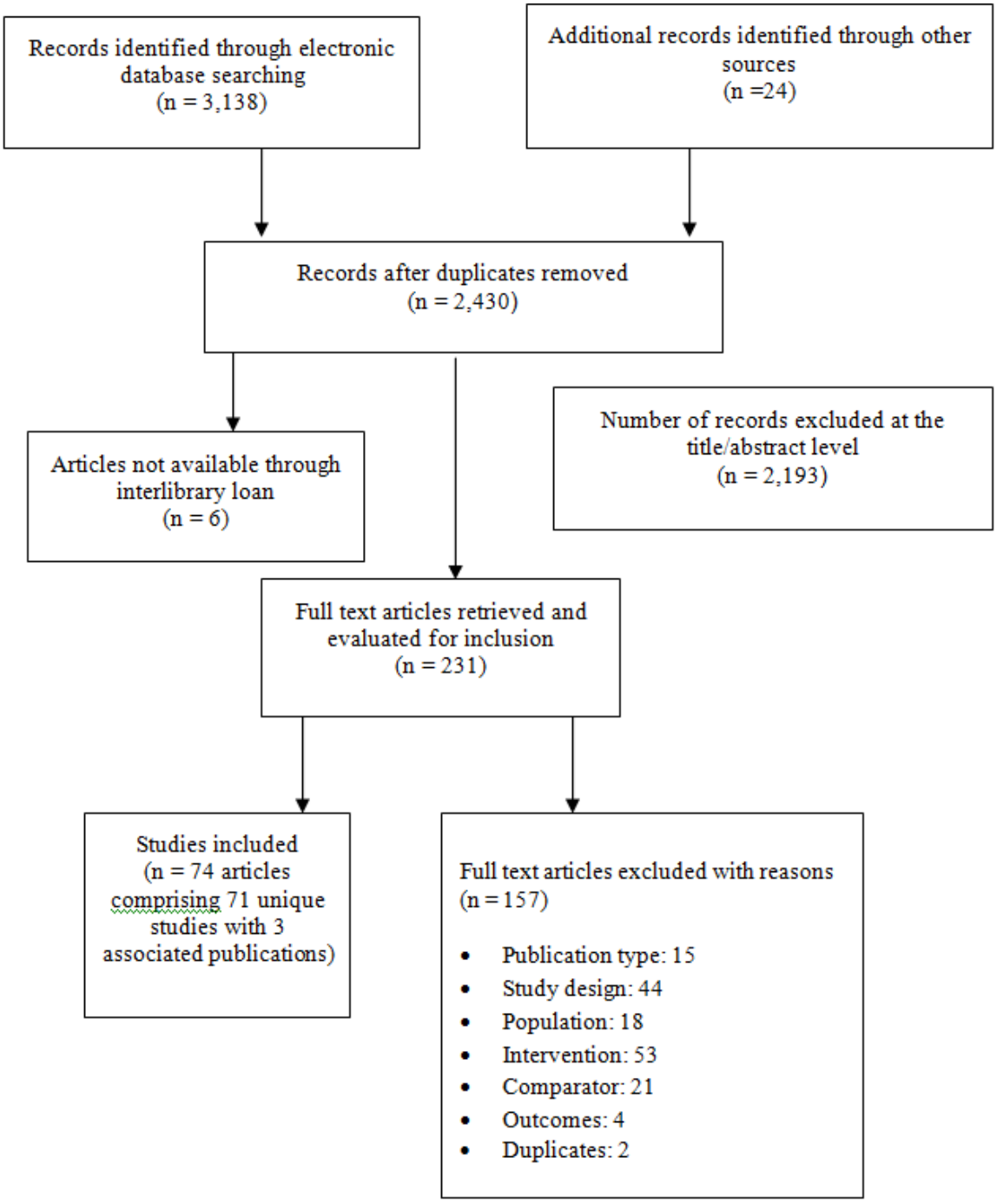
Metagraphs and tables reporting the strength of evidence for key outcomes are presented within each applicable section. Within each metagraph, the studies that provided data are identified by the name of the first author and year of publication. A list of acronyms is provided at the end of the report.

Literature Search

The search identified 3,138 citations from electronic databases. Screening based on titles and abstracts, grey literature searches, and hand searching identified 231 potentially relevant studies that were evaluated for inclusion. Using a standardized inclusion–exclusion form (Appendix B), 71 studies (and three companion 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 69 randomized controlled trials (RCTs) and 2 nonrandomized controlled trials (NRCTs) in the review. One of the included studies had three associated publications. Three studies were published in non-English language journals; the articles were translated and data 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 71 unique studies (69 RCTs and 2 NRCTs) that met the eligibility criteria. Nine different classes of drugs were investigated: antiemetics (metoclopramide), neuroleptics, ergotamines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, triptans, magnesium sulfate ($MgSO_4$), and anithistamines. In addition, there were several studies that examined combinations of active agents compared with other active agents. For the mixed

treatment analysis, we identified a group of drugs that were not easily classified and were infrequently studied (i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide). We collectively referred to these drugs as "orphan agents".

Most trials were of parallel design; three used a cross-over design. Most trials (60, 85 percent) had two study arms. Seven trials (10 percent) had three study arms, and four (6 percent) had four study arms. One study[41] described a five armed trial where the efficacy of metamizole, diclofenac, chlorpromazine, $MgSO_4$ and placebo were compared. Since this publication did not provide any extractable data, we included three associated publications that compared the placebo arm with diclofenac,[42] chlorpromazine,[43] and $MgSO_4$.[44] We did not include the publication on metamizole (dipyrone) since this drug is banned in the United States. In the body of this review, we only cite the three publications from which data were extracted.

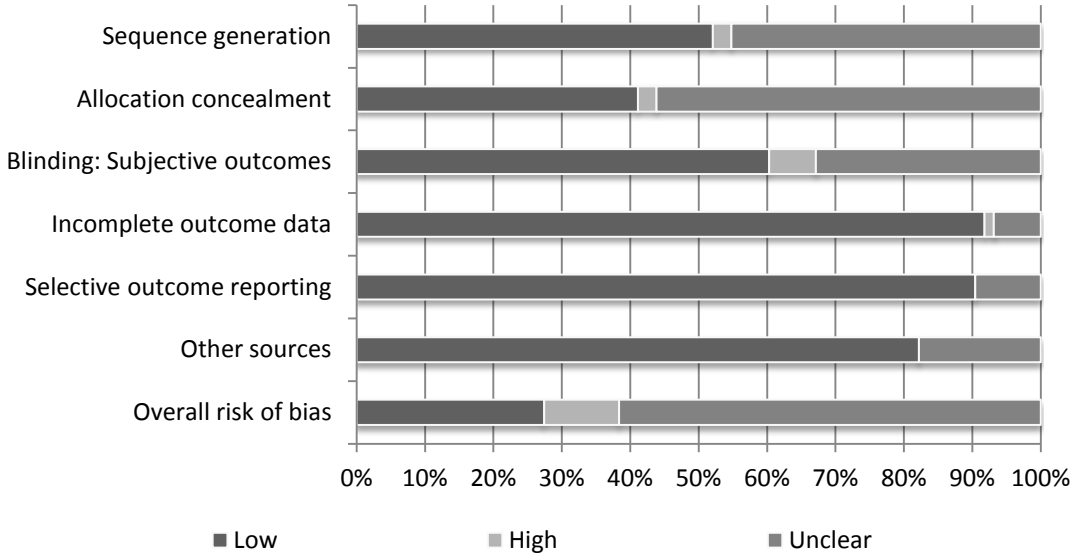
Evidence tables that describe the studies in more detail are presented in the results section. The studies were published between 1986 and 2011 (median = 2001 [interquartile range (IQR), 1993 to 2004]). The majority of studies were conducted in the United States (62 percent). The rest were conducted in Canada (13 percent), Turkey (8 percent), and other countries (15 percent). The most commonly reported measure of pain was the visual analogue scale (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 and 2 cm (10–20 mm) on the VAS is considered clinically significant.[45-51] In 43 studies (61 percent) migraine was classified using the criteria established by the International Headache Society.

Methodological Quality of Included Studies

A summary of the risk of bias assessments is presented in Figure 3; the detailed consensus assessments are presented in Appendix D. Overall, 60.6 percent (n = 43) of the trials had an unclear risk of bias, 28.2 percent (n = 20) had low risk, and 11.0 percent (n = 8) 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.

Twelve studies were funded by industry,[52-63] seven were funded by associations and foundations,[19,20,64-68] one received government funding,[69] and two had other sources of funding.[70,71] Funding was not reported by 47 (68 percent) studies.[21,22,29,32,42,43,72-112]

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

The findings for KQ 1 are presented by drug class, comparing the drug class with placebo, if applicable, and then with other active agents. Note that some studies included both head to head and placebo comparisons and appear in both sections. For studies that assessed antiemetics, all but one[79] examined metoclopramide. Therefore, we titled the section "Metoclopramide". As appropriate, we highlight the outcomes that include results from the study that assessed the combination of trimethobenzamide and diphenhydramine.[79]

Metoclopramide

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).
- Single trials assessed headache recurrence and headache relief for patients who received metoclopramide compared with placebo (insufficient strength of evidence).
- There was insufficient strength of evidence for improvement in pain intensity (VAS) for patients who received metoclopramide in combination with either dihydroergotamine (DHE) or dexamethasone.
- In general, neuroleptics were more effective than metoclopramide for pain relief based on four trials (low strength of evidence).
- There was no statistically significant difference in change in pain intensity (VAS) for patients receiving metoclopramide compared with prochlorperazine based on two RCTs (low strength of evidence).

- For all other head to head comparisons, single trials compared metoclopramide with another active agent for headache relief, pain free response, headache response, and headache recurrence at various timepoints (insufficient strength of evidence).

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. See Table 6 for details on study and patient characteristics.

Metoclopramide Versus Placebo

Description of Included Studies

Six RCTs[83,91,92,95,107,113] assessed the effectiveness of metoclopramide compared with placebo. One three-armed trial[107] compared a combination of metoclopramide plus dihydroergotamine (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,[91] the secondary outcomes were adverse effects or ability to function.

Two studies had a low risk of bias;[83,91] the remaining four [92,95,107,113] 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.

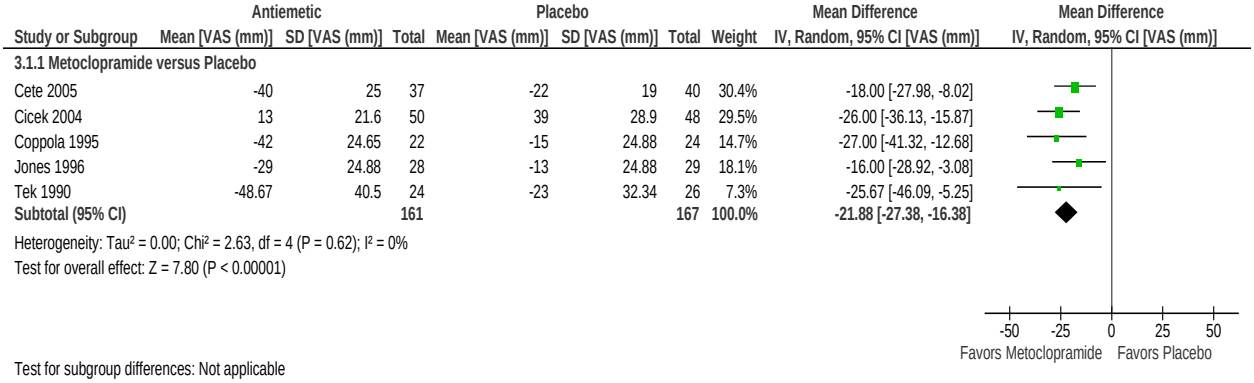
Metoclopramide Monotherapy Versus Placebo

Five RCTs[83,91,92,95,113] assessed metoclopramide monotherapy compared with placebo. In each study, participants were administered 10 mg of metoclopramide.

Change in Pain Intensity (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



VAS = visual analogue scale

Headache Relief

One study[95] 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[91] and reported that significantly more patients receiving metoclopramide experienced relief compared with those who received placebo (RR = 4.19; 95% CI: 1.35, 13.03).

Headache Recurrence

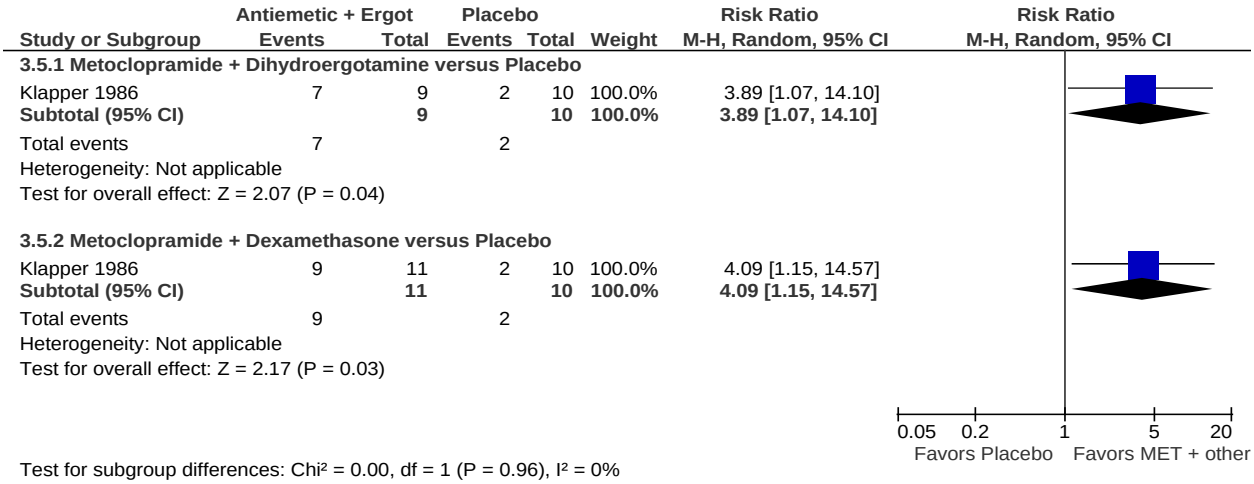
Patients in one study were contacted 24 hours after discharge from the ED to determine headache recurrence.[83] A lower proportion of patients who received metoclopramide experienced recurrence of headache (16/37) compared with those who received placebo (21/40); however, the difference between groups 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.[107] Participants were administered 5 to 10 mg of metoclopramide. 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 in combination with other active agents and placebo



Return to Normal Functioning

In one study[107] 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.

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 relief (1; 50)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache recurrence (1; 77)	Low	Unknown	Direct	Imprecise	Insufficient
Metoclopramide+ DHE or dexamethasone vs. placebo	Pain improvement (1 RCT [3 arms]; 20)	Moderate	Unknown	Direct	Precise	Insufficient

DHE = dihydroergotamine; N = number; ROB = risk of bias; RCT = randomized control trial; VAS = visual analogue scale

Metoclopramide Versus Active Agents

Description of Included Studies

Eight RCTs and one NRCT[22,65,79,82,83,91,92,105,113] assessed the effectiveness of metoclopramide versus other active agents. Of these, four[22,65,91,92] specifically compared metoclopramide with 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 studies had a pain related primary outcome (e.g., 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[65,79,83,91] had a low risk of bias, while five[22,82,92,105,113] had an unclear risk of bias (Appendix D).

Effectiveness Results

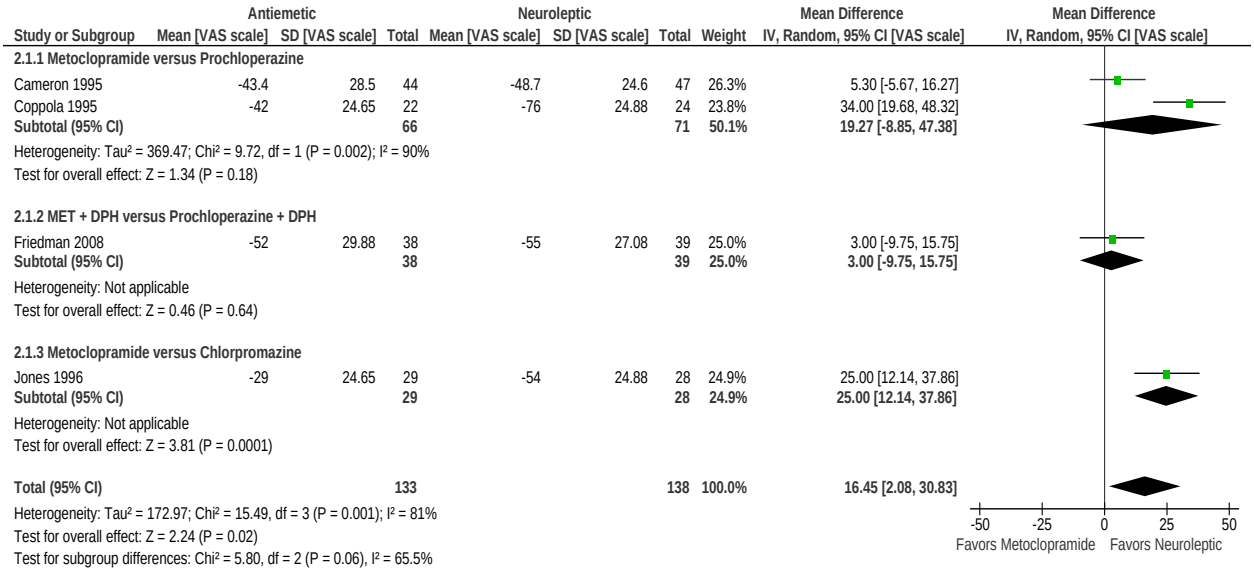
Metoclopramide Versus Neuroleptics

Three studies[65,91,92] 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.[22] Participants were administered 0.1 mg/kg,[65] 10 mg,[91,92] and 20 mg[22] of metoclopramide.

Change in Pain Intensity (VAS)

All four studies reported change in pain scores as measured on the VAS (mm) (Figure 6).[22,65,91,92] Results were consistent across studies in favor of neuroleptic agents. Two studies compared metoclopramide monotherapy with prochlorperazine.[65,92] 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%).[92] Statistically significant results favoring the neuroleptic were found in the one study comparing chlorpromazine with metoclopramide (MD = 25.0; 95% CI: 12.14, 37.86).[91] In the study where the antihistamine diphenhydramine was administered to both the metoclopramide and prochlorperazine groups, the differences in pain scores were not statistically significant.[22] The pooled results are statistically significant in favor of the neuroleptic agents (MD = 16.45; 95% CI: 2.08, 30.83; I^2 = 81%).

Figure 6. Change in pain (VAS) in trials comparing metoclopramide and neuroleptics



VAS = visual analogue scale

Severe Headache Recurrence

In one study,[65] patients were contacted by a nurse by telephone 48 hours post discharge to evaluate recurrence of headache. Patients who received metoclopramide had less headache recurrence compared with patients who received prochlorperazine; however, the results were not statistically significant (RR = 0.41; 95% CI: 0.11, 1.51).

Relief of Nausea and Vomiting

One study[91] 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.[22] 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.

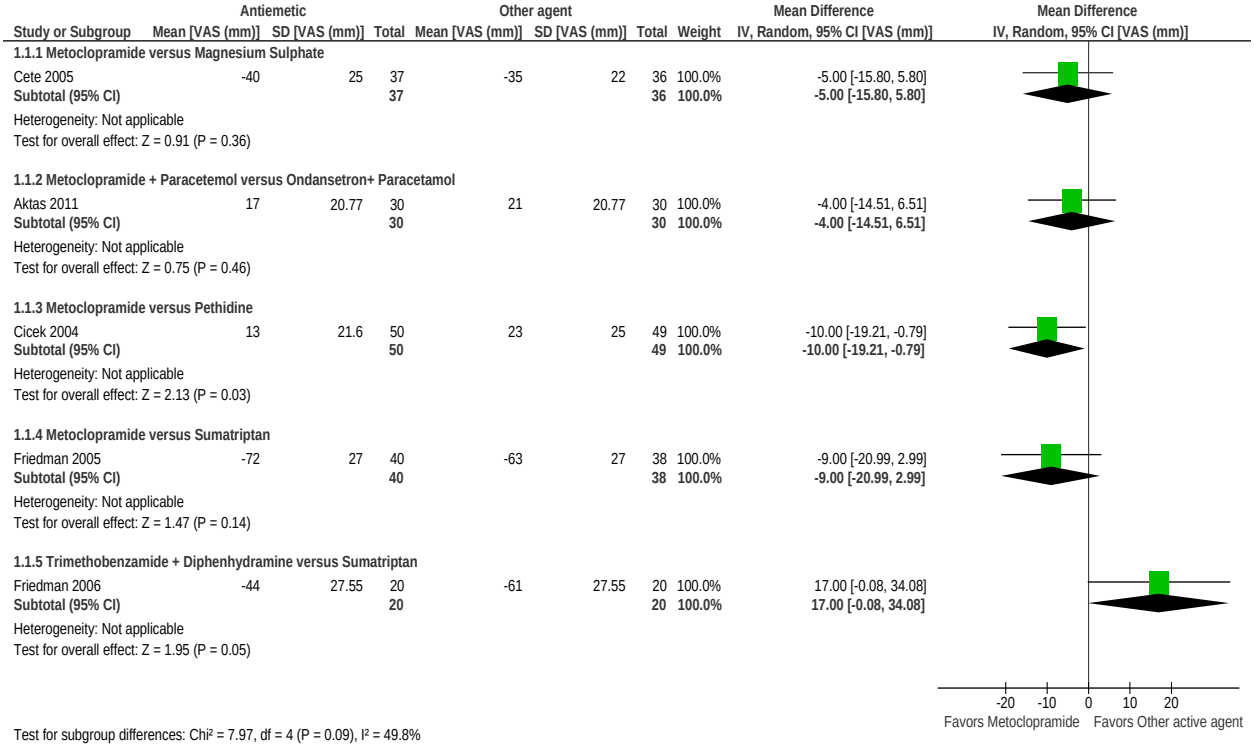
Metoclopramide Versus Other Active Agents (Excluding Neuroleptics)

Four studies investigated the efficacy of metoclopramide compared with other active agents including: $MgSO_4$,[83] ondansetron plus paracetemol,[105] pethidine,[113] and sumatriptan.[82] In one study the dose of metoclopramide was 20 mg;[82] in the other four studies the dose was 10 mg. In one study, trimethobenzamide plus diphenhydramine was compared with sumatriptan.[79]

Change in Pain Intensity (VAS)

Five studies[79,82,83,105,113] measured pain or change in pain intensity using the VAS (mm) (Figure 7). In the figure, a negative number is a 'change from baseline' while a positive is a final pain score. Results were inconsistent across studies. While three studies reported nonsignificant pain or change in pain intensity,[79,83,105] one study reported a statistically significant difference favoring metoclopramide versus pethidine.[113] The results of the study that compared trimethobenzamine and diphenhydramide with sumatriptan showed that sumatriptan was more effective but the difference was not statistically significant.[79]

Figure 7. Change in pain intensity (<2 hours) (VAS) in trials comparing metoclopramide and other active agents (excluding neuroleptics)



VAS = visual analogue scale

Headache Recurrence

One study measured headache recurrence at 24 hours and found no statistically significant difference between metoclopramide and $MgSO_4$[83] (RR = 0.82; 95% CI: 0.51, 1.33)

Other Outcomes

One study assessed the administration of paracetemol with both metoclopramide and ondansetron.[105] 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.[79] 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	Change in pain–VAS (4; 271)	Moderate	Inconsistent	Direct	Precise	Low
Metoclopramide vs. prochlorperazine	Change in pain–VAS (2; 137)	Moderate	Consistent	Direct	Imprecise	Low
	Headache recurrence (1; 91)	Low	Unknown	Direct	Imprecise	Insufficient
Metoclopramide vs. prochlorperazine + DPH	Change in pain–VAS (1; 77)	Moderate	Unknown	Direct	Imprecise	Insufficient
Metoclopramide vs. chlorpromazine	Change in pain–VAS (1; 57)	Low	Unknown	Direct	Precise	Insufficient
Metoclopramide + DPH vs. prochlorperazine + DPH	Sustained headache relief (24 hrs) (1; 77)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Pain free (2 hrs) (1; 77)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief (2hrs) (1; 77)	Moderate	Unknown	Direct	Imprecise	Insufficient
Metoclopramide vs. $MgSO_4$	Change in pain (<2 hrs)–VAS (1; 73)	Low	Unknown	Direct	Imprecise	Insufficient
	Headache recurrence (1; 73)	Low	Unknown	Direct	Imprecise	Insufficient
Metoclopramide + paracetemol vs. ondansetron + paracetamol	Change in pain (<2 hrs)–VAS (1; 60)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Change in pain intensity at 24 hrs–NRS (1; 60)	Moderate	Unknown	Direct	Imprecise	Insufficient
Metoclopramide vs. pethidine	Change in pain (<2 hrs)–VAS (1; 99)	Moderate	Unknown	Direct	Precise	Insufficient
Metoclopramide vs. sumatriptan	Change in pain (<2 hrs)–VAS (1; 78)	Moderate	Unknown	Direct	Imprecise	Insufficient
Trimethobenzamide + DPH vs. sumatriptan	Change in pain (<2 hrs)–VAS (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Pain free response (1 hr) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Pain free response (2 hr) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Pain free response (24 hrs) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Headache response (1 hr) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Headache response (2 hr) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Headache response (24 hrs) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient

DPH = diphenhydramine; $MgSO_4$ = magnesium sulfate; N = number; NRS = numerical rating scale; ROB = risk of bias; VAS = visual analogue scale

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

Comparison	Author, Year, Country Study Fesign	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[83]	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[113]	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, 1995, U.S., RCT[92]	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[91]	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

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

Comparison	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 (continued)	Klapper, 1989, U.S., RCT[107]	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 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)
	Tek, 1990, U.S., RCT[95]	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[65]	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[92]	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

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

Comparison	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. neuroleptics (continued)	Friedman, BW, 2008, U.S., RCT[22]	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 [91]	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
Metoclopramide versus other active agents	Aktas, 2011, Turkey, NRCT[105]	60 min, (NA)	G1: Ondansetron + Paracetamol, n=30, 4mg Ondansetron IV + 1g Paracetamol IV G2: MET+ Paracetamol, n=30, 10mg MET 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) 2: additional analgesia, mean durations of ED stay

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

Comparison	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 versus other active agents (continued)	Cete, Y, 2004, Turkey, RCT[83]	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[113]	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[82]	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

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

Comparison	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 versus other active agents (continued)	Friedman, BW, 2006, U.S., RCT[79]	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 >24 hr, rescue therapy, nausea, limitation to usual daily activities

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 sulfate; 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 neuroleptic agents 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 neuroleptic agents had greater headache relief at 1 hour compared with those receiving placebo based on five RCTs (moderate strength of evidence).
- Fewer patients who received neuroleptic agents experienced headache recurrence compared with those receiving placebo based on two RCTs (low strength of evidence).
- More patients who received droperidol experienced headache relief compared with patients who received prochlorperazine based on two RCTs (moderate strength of evidence).
- For all other head to head comparisons, single trials compared a neuroleptic agent with another active agent for headache relief, pain free response, headache response, and headache recurrence at various timepoints (insufficient strength of evidence).

Results

The results from studies that compared neuroleptics with placebo or with other active agents are presented below. Note that the studies that specifically compared neuroleptics and metoclopramide were described previously in the metoclopramide section. Table 7 and Table 8 provide the strength of evidence grades for all key outcomes. See Table 9 for details on study and patient characteristics.

Neuroleptic Agents Versus Placebo

Description of Included Studies

Seven RCTs[43,63,68,80,91,92,97] and one NRCT[90] evaluated the effectiveness of neuroleptics versus placebo. The neuroleptics included prochlorperazine,[68,90-92] chlorpromazine,[43,97] haloperidol,[80] and droperidol.[63] Most trials took place in the ED; one took place in a headache clinic.[63] The mean ages of the participant groups ranged from 29.6 and 41.0 years; age was not reported in one study.[92] In seven studies, the majority of patients were female; in one study, 40 percent of the placebo group was female.[90] Race or ethnicity was not reported in any of the studies. The primary outcomes were pain related,[43,63,68,80,91,92] incidence of akathisia,[90] and response to treatment.[97] Secondary outcomes included therapeutic gain, nausea, vomiting, sedation, treatment failures, and successful treatment response or therapeutic gain. The timepoints measured in the ED ranged from 30 minutes to 4 hours. The followup timepoints after discharge ranged from 24 hours to 1 month.

Two studies had a low risk of bias,[68,91] five[43,63,80,92,97] had an unclear risk of bias, and one[90] had a high risk of bias (Appendix D).

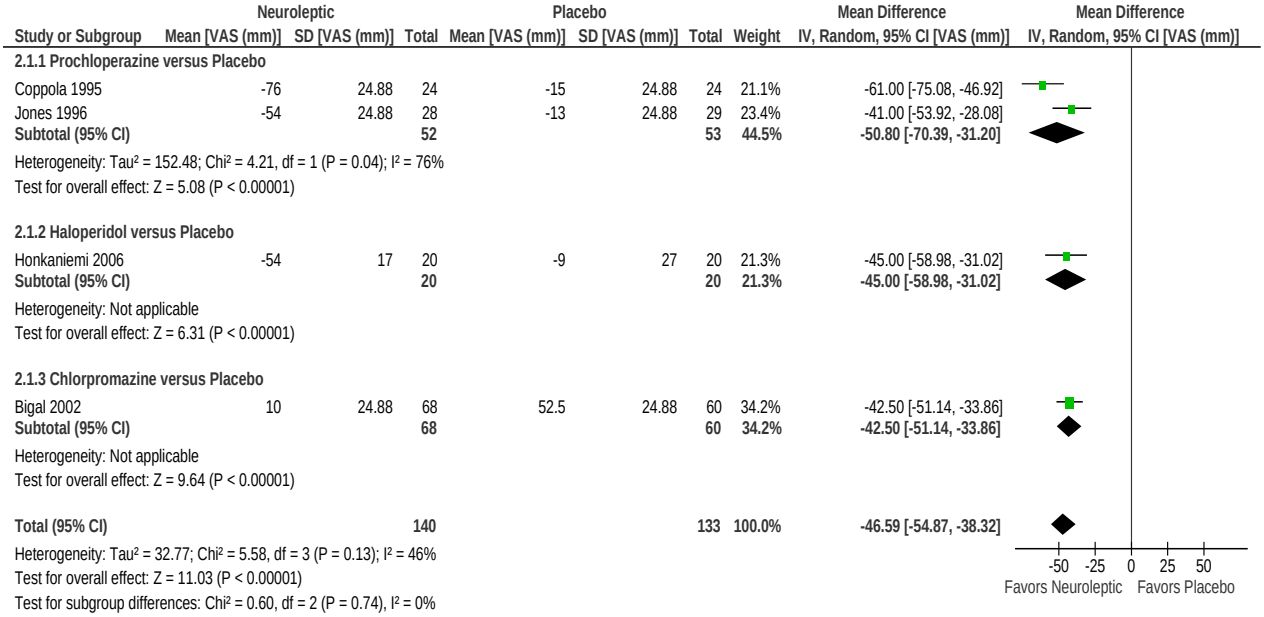
Effectiveness Results

Change in Pain Intensity (VAS)

The change in pain intensity was reported by change in VAS (Figure 8). The pooled result was statistically significant in favor of neuroleptics (MD = -46.59; 95% CI: -54.87, -38.32; I^2 =

46%).[43,80,91,92] In all but one study[43] authors reported pain as change from baseline (negative numbers); when these data were not reported, end of study data were presented (positive numbers).

Figure 8. Change in pain intensity (VAS) in trials comparing neuroleptics and placebo



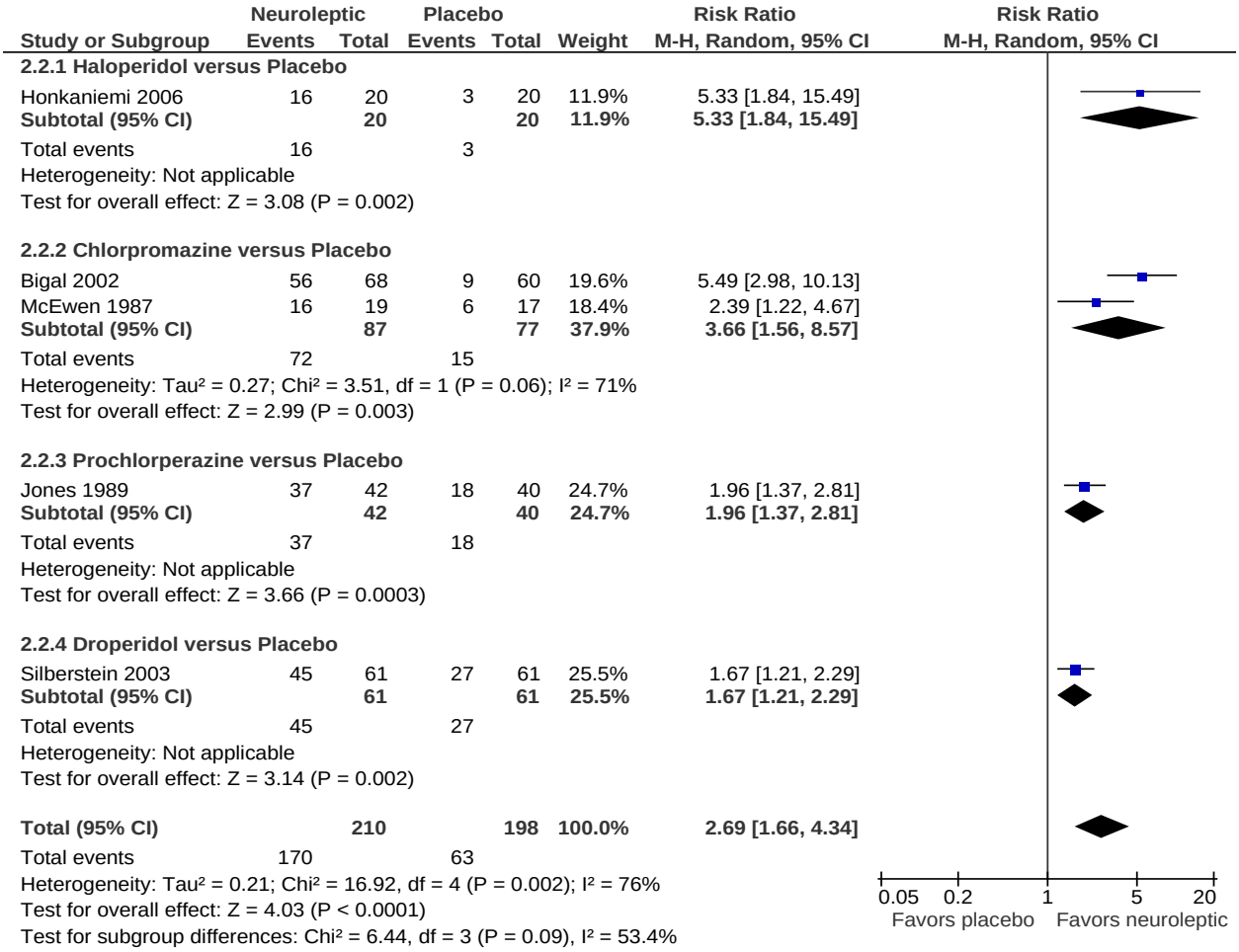
VAS = visual analogue scale

Headache Relief (1-2 hours)

Five studies evaluated relief of headache at 1 hour (Figure 9).[43,63,68,80,97] All studies reported a statistically significant result in favor of the neuroleptics; the pooled result was RR = 2.69 (95% CI: 1.66, 4.34; I^2 = 76%). In two studies, the neuroleptic used was chlorpromazine.[43,97] In one study[43] patients were given an IV injection of 5.0 ml/kg 0.9 percent normal saline solution followed by IV chlorpromazine, 0.1 mg/kg diluted to 10 ml of 0.9 percent normal saline. In the remaining studies, patients were administered 50 mg/2ml of chlorpromazine[97] or 2.75 mg droperidol.[63]

One study assessed headache response at 2 hours.[63] Significantly more participants who received droperidol experienced relief of pain at 2 hours (RR = 1.51; 95% CI: 1.19, 1.92).

Figure 9. Headache relief (1 hour) in trials comparing neuroleptics and placebo

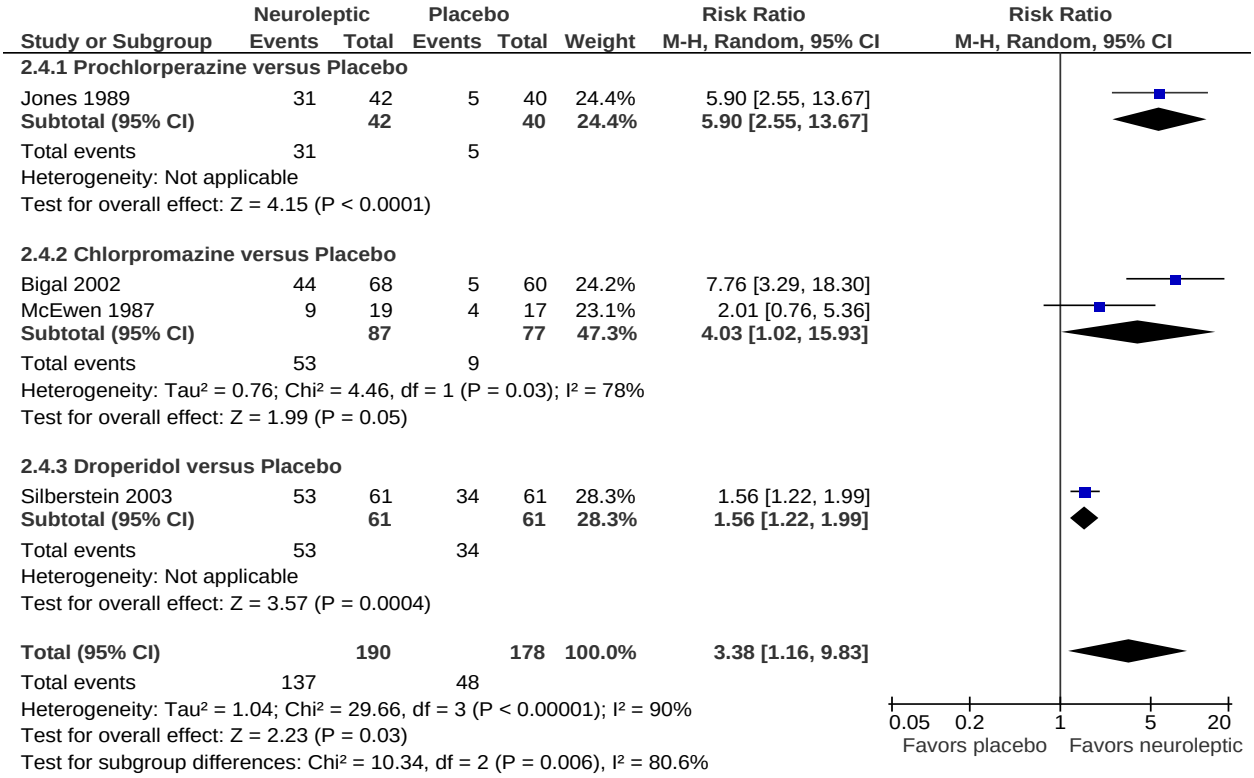


Pain Free (1 hour)

Four studies reported on pain free status of participants at 1 hour (Figure 10).[43,63,68,97] The pooled results of two studies[43,97] 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 was statistically significant in favor of the neuroleptics (RR = 3.38; 95% CI: 1.16, 9.83; I^2 = 90%).

Pain free status was also measured at 2 hours in one study.[63] The results were statistically significant in favor of droperidol versus placebo (RR = 2.11; 95% CI: 1.37, 3.26).

Figure 10. 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.[43] In this study, 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).[43] Another study[63] recorded the number of patients whose headache improved at 2 hours but recurred within 24 hours. There was no significant difference in the rates of headache recurrence for those who received droperidol and those who received placebo (RR = 0.69; 95% CI: 0.43, 1.12). The pooled results favor neuroleptics, however, the difference was not statistically significant (RR = 0.46; 95% CI; 0.19, 1.10; I^2 = 78%).

Nausea and Vomiting

One study assessed relief of nausea and vomiting 60 minutes after the administration of prochlorperazine or placebo.[91] Participants who received prochlorperazine experienced significantly greater relief than those who received placebo (RR = 5.89; 95% CI: 1.98, 17.57). One study reported the percentage of patients who experienced nausea and vomiting 2 hours post-treatment.[63] The difference between the droperidol and placebo groups was not statistically significant for either nausea or vomiting (RR = 0.36; 95% CI: 0.12, 1.08 and RR = 0.33; 95% CI: 0.01, 8.03, respectively).

Patient Satisfaction

One study reported patient dis-satisfaction as the number of patients who asked for a second drug at the end of 1 hour.[97] 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).

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
	Headache relief at 1 hr (5; 408)	Moderate	Consistent	Direct	Precise	Moderate
	Pain free at 1 hr (4; 368)	Moderate	Consistent	Direct	Precise	Moderate
	Headache recurrence (2; 250)	Moderate	Inconsistent	Direct	Imprecise	Low
	Patient satisfaction (1; 36)	Moderate	Unknown	Direct	Precise	Insufficient

N = number; ROB = risk of bias; VAS = visual analogue scale

Neuroleptic Agents Versus Active Agents

Description of Included Studies

There were 17 RCTs[29,54,64,66,67,69-71,73-75,85,87-89,96,114] that assessed the effectiveness of neuroleptics versus other active agents. The neuroleptics included prochlorperazine,[29,64,69-71,73,75,87-89] chlorpromazine,[54,67,96] haloperidol,[114] droperidol,[85] methotrimeptrazine,[66] and olanzapine.[74] One study was a three-arm trial that compared chlorpromazine, DHE, and lidocaine.[96] The active comparators included anticonvulsants (sodium valproate and $MgSO_4$),[69,89] dexamethasone,[114] DHE,[96] neuroleptics (droperidol and prochlorperazine),[29,70,74,87,88,96] NSAIDs (ketorolac and ketorolac tropethamine),[54,71] opioids (meperidine),[66,67,85] somatostatin analog,[73] sumatriptan,[64] and lidocaine.[88]

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.[64,69,71,74,75,85,88,89] The number of participants who were randomized ranged from 29 to 168 (median = 64; IQR: 40, 82). The mean age of patients ranged from 27 to 35 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 pain scores.[54] Secondary outcomes varied across studies and included headache recurrence, patient satisfaction, nausea, and sedation.

Seven studies had low risk of bias,[29,54,64,66,69,88,89] nine had an unclear risk of bias,[67,70,71,73-75,85,87,114] and one had a high risk of bias[96] (Appendix D).

Effectiveness Results

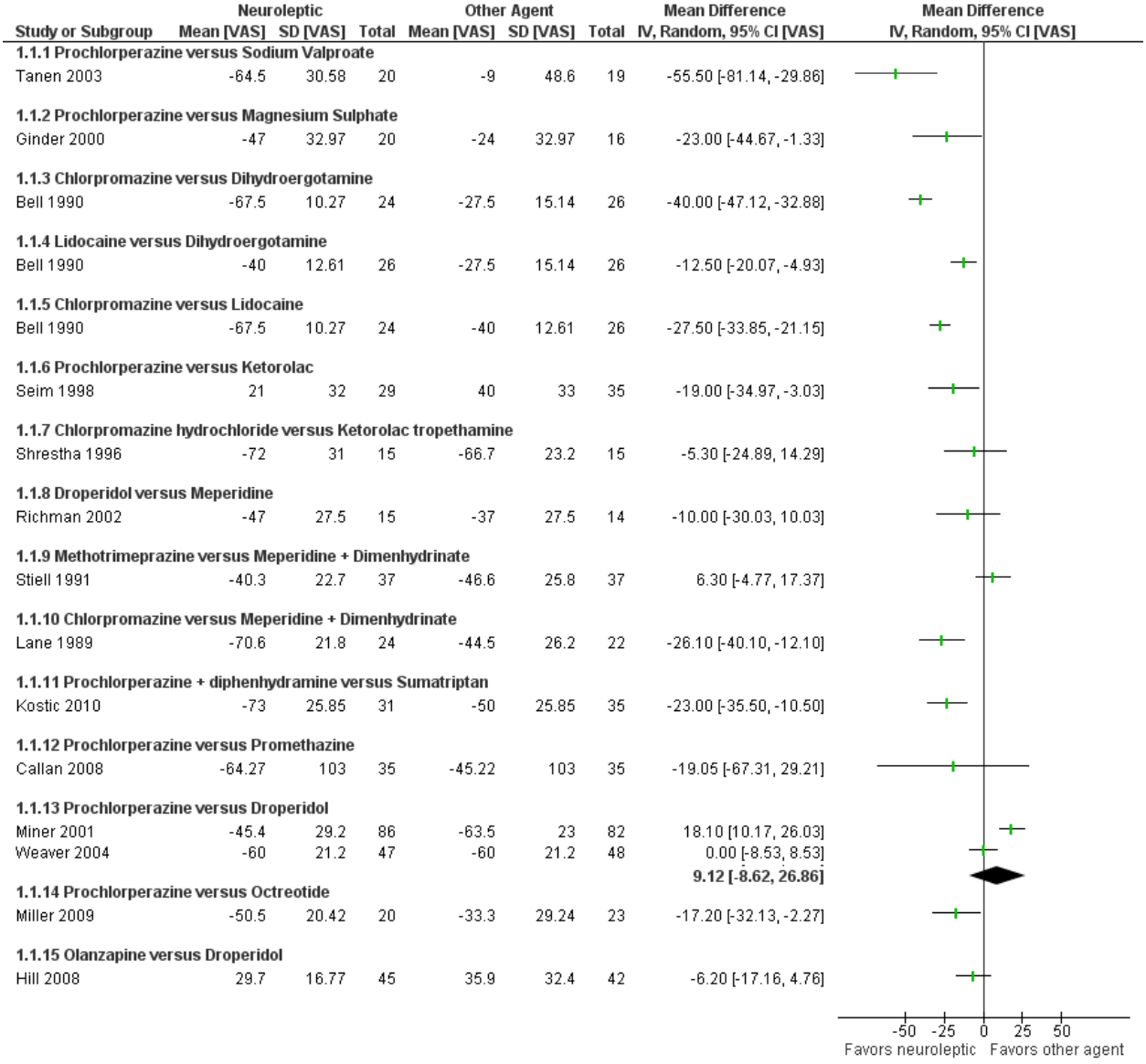
Change in Pain Intensity (VAS)

Fourteen studies reported change in pain scores. Twelve studies specifically stated that pain was measured using the VAS (mm).[54,66,67,69,71,85,89,64,73-75,87] One reported using a headache scale ranging from 1 to 10,[96] while another used the Wong-Baker Faces Rating Scale.[54]

Eight studies[64,67,69,71,73,87,89,96] reported statistically significant results in favor of the neuroleptic agents (Figure 11). In four studies the neuroleptic was favored over the other active

agent, although the differences were not statistically significant.[54,74,75,85] In one study, the participants who received meperidine plus dimenhydrinate experienced more improvement in pain scores compared with those who received methotrimeptrazine; however, the difference was not statistically significant.[66] We did not pool the results due to statistical and clinical heterogeneity.

Figure 11. Change in pain (VAS) in trials comparing neuroleptics and active agents



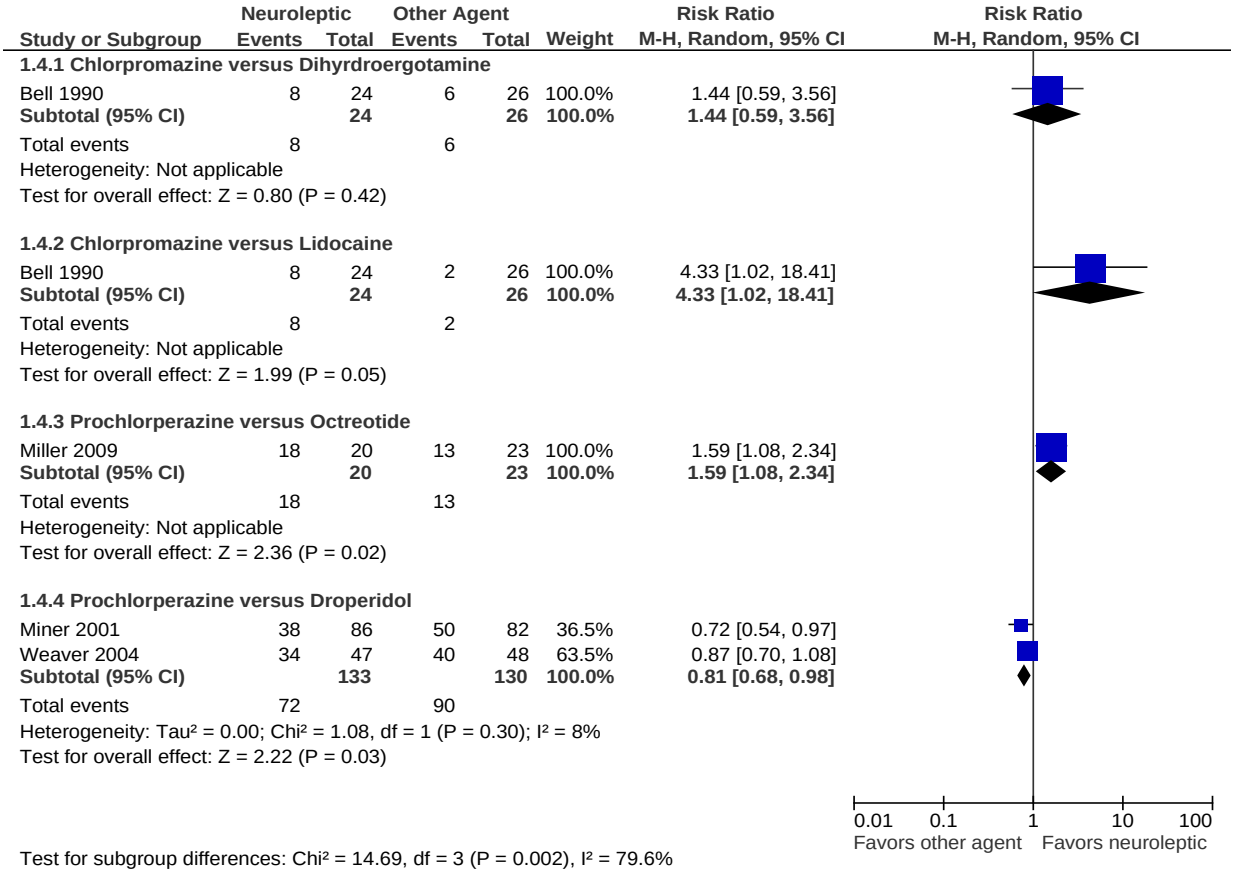
VAS = visual analogue scale

Headache Relief

Headache relief was evaluated in four studies (Figure 12).[70,73,87,96] One of the trials had three study arms in which chlorpromazine, DHE, and lidocaine were compared.[96] In one study, significantly more participants in the prochlorperazine group experienced headache relief compared with those in the octerotide group (RR = 1.59; 95% CI: 1.08, 2.34).[73] In the two studies comparing prochlorperazine with droperidol, one study did not report a signifiant

difference between groups,[70] while the other study showed a statistically significant difference favoring droperidol.[87]

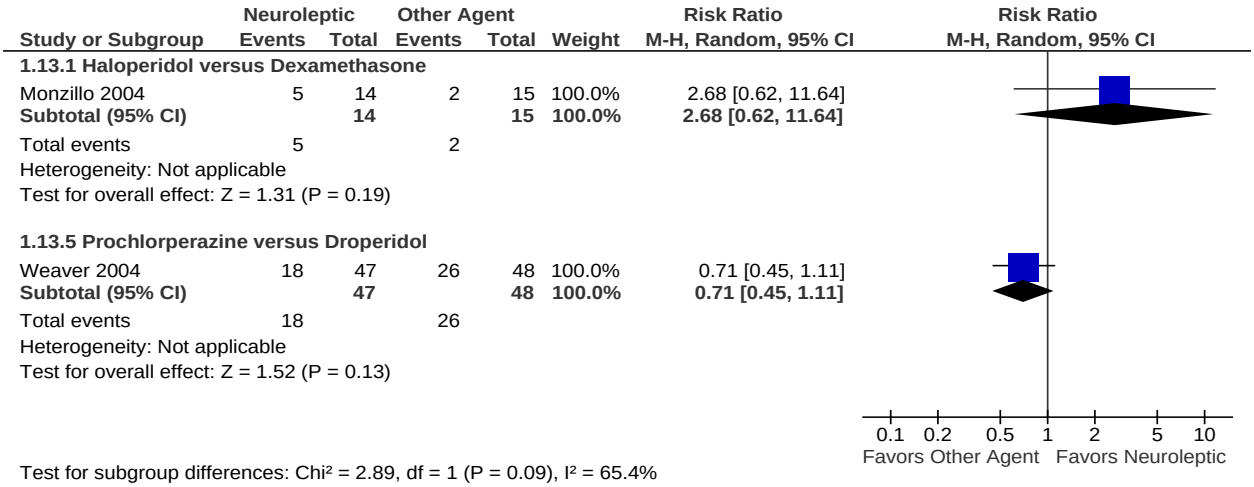
Figure 12. Headache relief in trials comparing neuroleptics and active agents



Pain Free at 30 Minutes

Two studies reported the number of patients who were pain free 30 minutes after administration of the interventions (Figure 13).[70,114] In one study, haloperidol was found to be more effective than dexamethasone,[114] while in the other study more people in the droperidol group were free from pain at 30 minutes compared with those in the prochlorperazine group.[70] 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).[114]

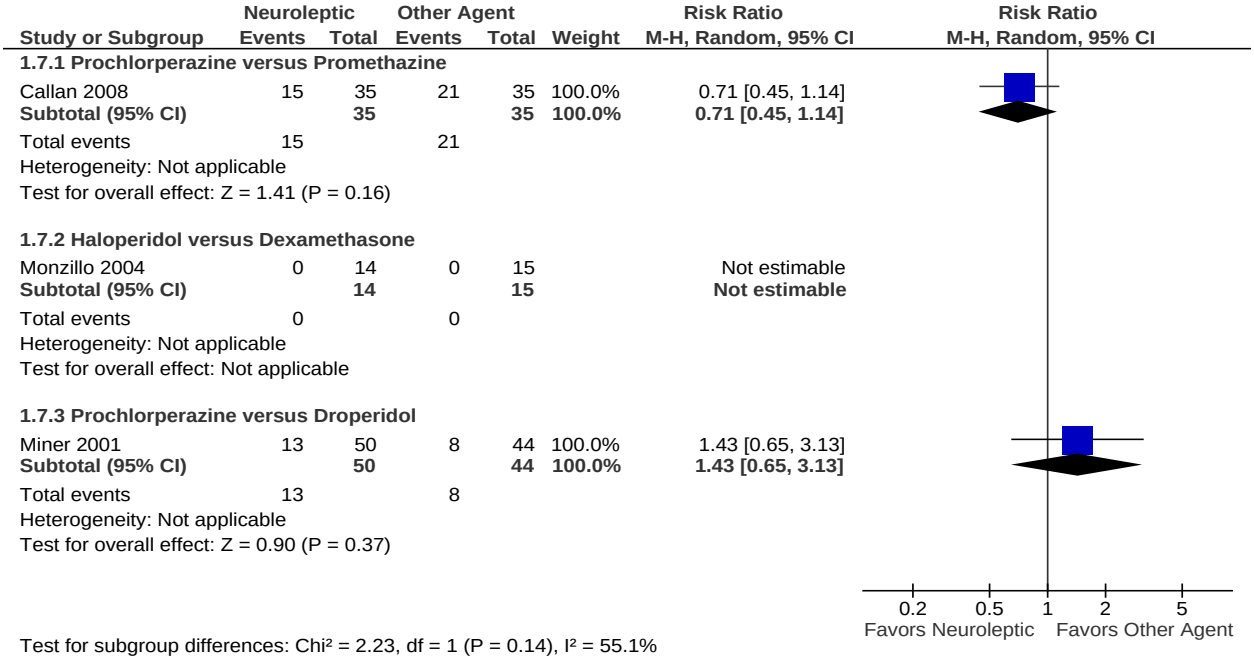
Figure 13. Pain free at 30 minutes in trials comparing neuroleptics and active agents



Headache Recurrence

Three studies assessed headache recurrence 24 hours after discharge (Figure 14).[75,87,114] In the study comparing haloperidol with dexamethasone, no patients in either group reported a recurrent headache.[114] There were no statistically significant differences between groups for proclorperazine versus promethazine,[75] or prochlorperazine versus droperidol.[87]

Figure 14. Headache recurrence in trials comparing neuroleptics and active agents



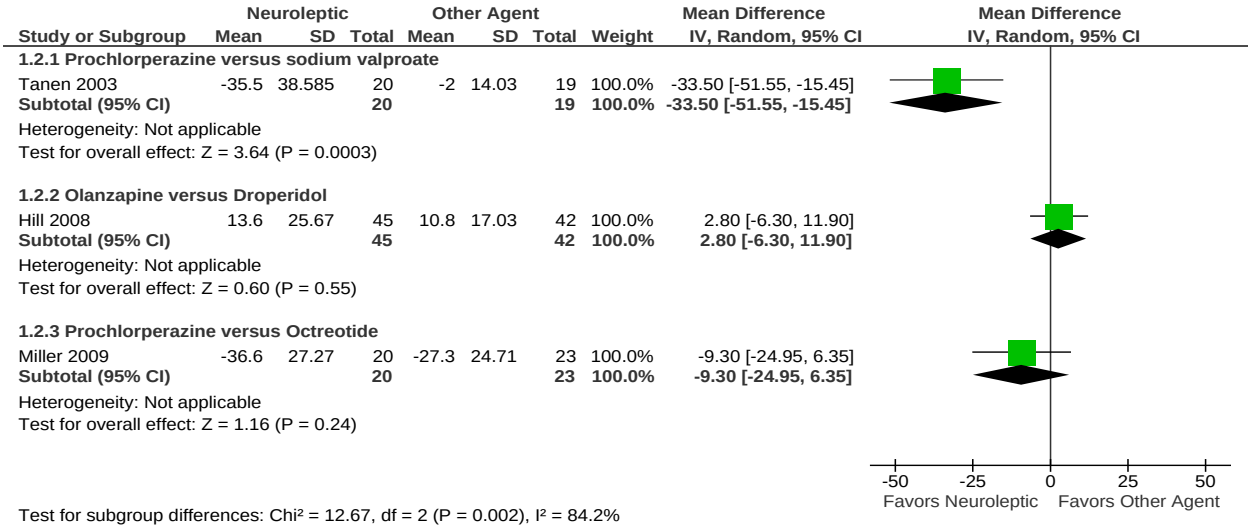
Patient Satisfaction

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).[75]

Nausea

Three studies assessed the effect of a neuroleptic versus another active agent on nausea as a symptom of migraine (Figure 15).[69,73,74] 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).[69]

Figure 15. Nausea in trials comparing neuroleptics and active agents

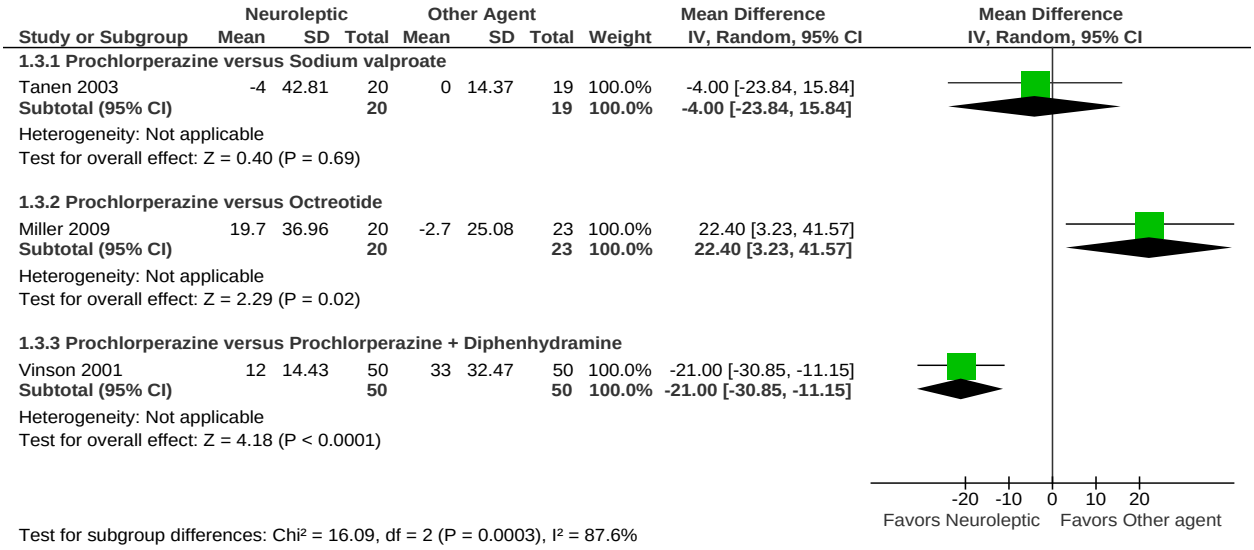


One study reported no statistically significant difference between methotrimetprazine and meperidine plus dimenhydrinate for residual nausea and vomiting (RR = 0.80; 95% CI: 0.36, 1.80).[66] In another study, resolution of nausea while in the ED was measured.[75] More patients who received prochlorperazine experienced nausea resolution compared with those receiving promethazine; the results were not statistically significant (RR = 1.34; 95% CI: 0.99, 1.83).

Sedation

Three studies assessed the reduction of migraine-related sedation (Figure 16).[29,69,73] One study favored octerotide over prochlorperazine (MD = 22.4; 95% CI: 3.23, 41.57).[73] In another study,[29] patients 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



More Than One Dose Required

One study reported no significant difference between those receiving chlorpromazine or meperidine and dimenhydrinate when comparing the need for another dose of medication (RR = 1.18; 95% CI: 0.80, 1.74).[67]

Other Outcomes

In one study, patients were contacted at home 1 day after discharge to determine rates of home drowsiness and agitation.[75] 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.

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	
Metoclopramide vs. neuroleptics	Change in pain–VAS (2; 271)	Moderate	Inconsistent	Direct	Precise	Low
Prochlorperazine vs. sodium valproate	Change in pain–VAS (1; 39)	Low	Unknown	Direct	Precise	Insufficient
Prochlorperazine vs. $MgSO_4$	Change in pain–VAS (1; 36)	Low	Unknown	Direct	Precise	Insufficient
Chlorpromazine vs. DHE	Change in pain–VAS (1; 50)	High	Unknown	Direct	Precise	Insufficient
	Headache relief (1; 50)	High	Unknown	Direct	Imprecise	Insufficient
Chlorpromazine vs. lidocaine	Change in pain–VAS (1; 50)	High	Unknown	Direct	Precise	Insufficient
	Headache relief (1; 50)	High	Unknown	Direct	Precise	Insufficient
Prochlorperazine vs. ketorolac	Change in pain–VAS (1; 64)	Moderate	Unknown	Direct	Precise	Insufficient

Table 8. Strength of evidence for neuroleptics versus active agents (continued)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Chlorpromazine hydrochloride vs. ketorolac tropethamine	Change in pain–VAS (1; 30)	Low	Unknown	Direct	Imprecise	Insufficient
Droperidol vs. meperidine	Change in pain–VAS (1; 29)	Moderate	Unknown	Direct	Imprecise	Insufficient
Methotrimeprazine vs. meperidine + dimenhydrinate	Change in pain–VAS (1; 82)	Low	Unknown	Direct	Imprecise	Insufficient
Chlorpromazine vs. meperidine + dimenhydrinate	Change in pain–VAS (1; 46)	Moderate	Unknown	Direct	Precise	Insufficient
Prochlorperazine + DPH vs. sumatriptan	Change in pain–VAS (1; 66)	Low	Unknown	Direct	Precise	Insufficient
Prochlorperazine vs. promethazine	Change in pain–VAS (1; 70)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache recurrence (1; 70)	Moderate	Unknown	Direct	Imprecise	Insufficient
Prochlorperazine vs. droperidol	Change in pain–VAS (2; 263)	Moderate	Inconsistent	Direct	Imprecise	Insufficient
	Headache relief (2; 263)	Moderate	Consistent	Direct	Precise	Moderate
	Pain free at 30 mins (1; 95)	Moderate	Unknown	Direct	Imprecise	Insufficient
Prochlorerpazine vs. octreotide	Change in pain–VAS (1; 44)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief (1; 43)	Moderate	Unknown	Direct	Precise	Insufficient
Olanzapine vs. droperidol	Change in pain–VAS (1; 87)	Moderate	Unknown	Direct	Imprecise	Insufficient
Haloperidol vs. dexamethasone	Pain free at 30 mins (1; 29)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache recurrence (1; 29)	Moderate	Unknown	Direct	Imprecise	Insufficient

DHE = dihydroergotamine; DPH = diphenhydramine; $MgSO_4$ = magnesium sulfate; N = number; NRS = numerical rating scale; ROB = risk of bias; VAS = visual analogue scale

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

Comparison	Author, Year, Country, Study Design	Timepoint 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 [43]	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
	Coppola, 1992, U.S., RCT [92]	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 [90]	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 [80]	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 [68]	60 min, (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

Table 9. Patient and study characteristics of trials comparing neuroleptics with placebo or other active agents (continued)

Comparison	Author, Year, Country, Study Design	Timepoint 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	Jones, 1996, U.S., RCT [91]	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 score (VAS) 2: nausea and vomiting
	McEwen, 1987, Canada, RCT[97]	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 2: successful tx response, measures of dissatisfaction
	Silberstein, 2003, U.S., RCT[63]	240min, (7d)	G1: DRO, n=61, 8.25mg IM P: Placebo, n=61, NR IM	G1: 42(10), 47(77.0), NR P: 44(9.7), 52(85.2), NR	G1: Moderate (64%), severe (36%); NR P: Moderate (56%), severe (44%), NR	1: 2 hr headache response and tolerability 2: headache assessment (other timepoints), pain-free response rates, recurrence, resolution of nonheadache symptoms, use of rescue medications
Neuroleptics versus active agents	Bell, 1990, Canada, RCT [96]	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)

Table 9. Patient and study characteristics of trials comparing neuroleptics with placebo or other active agents (continued)

Comparison	Author, Year, Country, Study Design	Timepoint 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 active agents (continued)	Blanda, 2001, U.S., RCT [88]	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 [75]	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 w/i 5 d, akathisia, rescue medication, patient satisfaction, drowsiness, agitation, nausea
	Ginder, 2000, U.S., RCT [89]	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 [74]	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 [64]	80 min (51 patients), (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

Table 9. Patient and study characteristics of trials comparing neuroleptics with placebo or other active agents (continued)

Comparison	Author, Year, Country, Study Design	Timepoint 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 active agents (continued)	Lane, 1989, Canada, RCT [67]	105min, (60 min)	G1: CPZ, n=24, 0.04ml (0.1 mg/kg)/kg IV G2: MEP + 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 [73]	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, nausea, sedation, occurrence of side effects (i.e., restlessness or akathisia)
	Miner, 2001, U.S., RCT [87]	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 [114] (Portugese)	120 min, (120 min)	G1: Haloperidol, n=14. 5 mg IV G2: DEX, n=15, 4 mg IV	Total: 31.5 (NR), 25 (86.2), NR	G1: NR, NR G2: NR, NR	1: pain intensity 2: pain recurrence, adverse effects
	Richman, 2002, U.S., RCT [85]	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 [71]	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)

Table 9. Patient and study characteristics of trials comparing neuroleptics with placebo or other active agents (continued)

Comparison	Author, Year, Country, Study Design	Timepoint 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 active agents (continued)	Shrestha, 1996, U.S., RCT [54]	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 [66]	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: % patients with relief of ≥7.0 cm on VAS, residual nausea or vomiting
	Tanen, 2003, U.S., RCT [69]	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 [70]	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)); Other	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

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; MEP = meperidine; MET = metoclopramide; mg = milligram(s); $MgSO_4$ = magnesium sulfate; 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).
- There was insufficient strength of evidence for headache recurrence for patients receiving NSAIDs versus placebo based on one RCT.
- For all head to head comparisons single trials compared NSAIDs with another active agent for change in pain (VAS), pain response, pain free at 1-2 hours, need for additional analgesia, and headache recurrence at various timepoints (insufficient strength of evidence).

Results

The results for studies that assessed nonsteroidal anti-inflammatory drugs (NSAIDs) are summarized below. Table 10, Table 11, and Table 12 present results or the strength of evidence grades for all key outcomes. See Table 13 for study and patient characteristics.

NSAIDs Versus Placebo

Description of Included Studies

Two RCTs assessed the effectiveness of NSAIDs compared with placebo in the treatment of acute migraine headaches.[42,100] The NSAIDs included lysine clonixinate[100] and diclofenac.[42] One study[100] was conducted in a headache clinic and one[42] was conducted in a public health clinic. The mean age of participant groups was 32 years in one study.[100] The participants were predominantly female and neither study reported the race or ethnicity of 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.

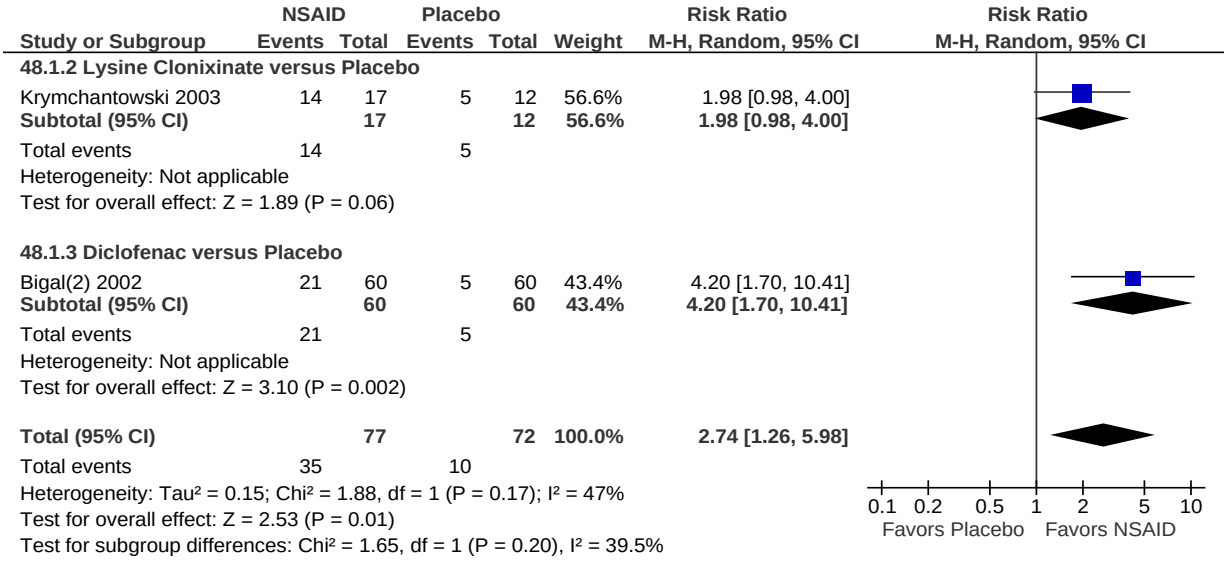
One study[42] had an unclear risk of bias, and the other[100] had a high risk of bias (Appendix D).

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[42,100] (Figure 17). The pooled results show that those who received NSAIDs experienced a greater decrease in pain intensity compared with those who received placebo (RR = 2.74; 95% CI: 1.26, 5.98; I^2= 47%).

Figure 17. Pain free at 1-2 hours in trials comparing NSAIDs and placebo



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.[42] The authors 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[42] 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[54-56,71,81,84,94,101,111] assessed the effectiveness of NSAIDs versus other active agents. The NSAIDs included ketorolac,[55,94,101] diclofenac[81,111] and lysine acetylsalicylic acid.[56] Comparators included meperidine monotherapy or in combination with other agents,[55,94,101] sumatriptan,[84] paracetamol,[111] ergotamine,[56] and tramadol.[81] Two studies have been described in another section of the report (neuroleptics) and compared NSAIDs with prochlorperazine[71] and chlorpromazine hydrochloride.[54]

All interventions were delivered in the ED, and assessments occurred between 60 and 180 minutes following administration. Followup ranged from 2 to 48 hours after patient discharge.

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 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.[54,71]

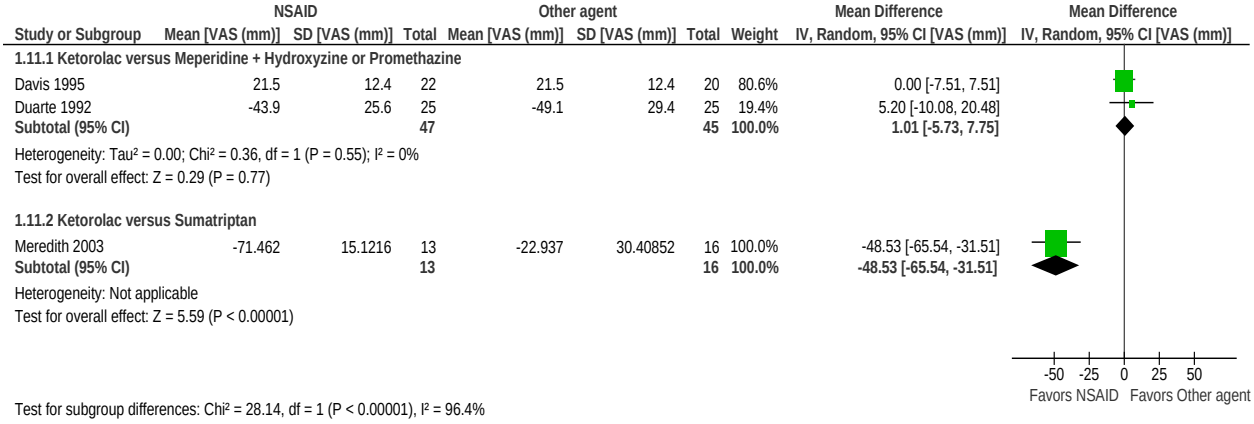
Two studies[54,81] had a low risk of bias, while the remaining seven studies had an unclear risk of bias (Appendix D).

Effectiveness Results

Pain Intensity (VAS)

Five studies[54,55,71,84,94] reported pain intensity using the VAS (mm) (Figure 18, Table 11). Table 8 describes the two studies that were analyzed in the neuroleptics section. All studies compared ketorolac with an active agent. One study[84] showed a significant difference in favor of ketorolac compared 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).[71] 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 8).

Figure 18. Pain intensity (VAS) in trials comparing NSAIDs and other active agents



VAS = visual analogue scale

Pain Response

Four studies reported a pain response after treatment (Figure 19).[55,56,81,101] One study [56] comparing lysine acetylsalicylic acid and ergotamine significantly favored NSAIDs (RR = 1.92; 95% CI: 1.10, 3.36). There was no statistically significant difference between NSAIDs and the other three active agents.[55,81,101] One study[81] also reported a pain response at 48 hours and found no difference between diclafenec and tramadol (RR = 0.92; 95% CI; 0.57, 1.49).

Figure 19. Pain response after treatment in trials comparing NSAIDs and other active agents

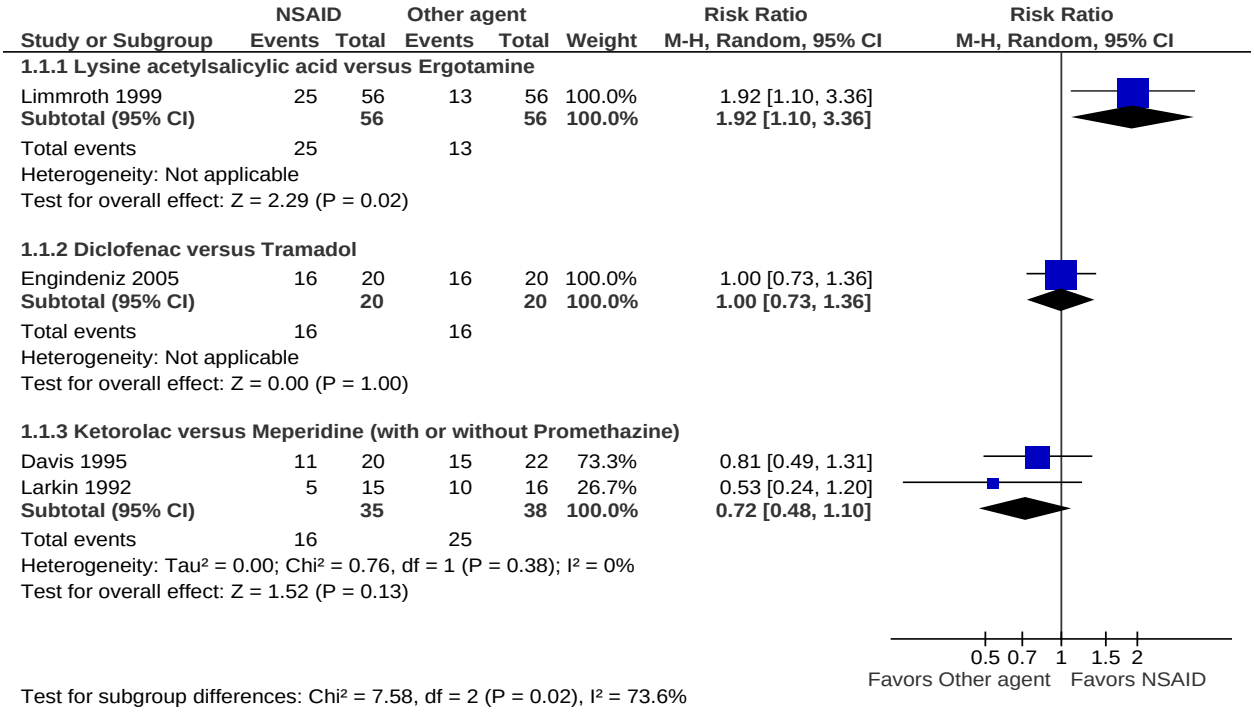


Table 11. Pain response after treatment in trials comparing NSAIDs and other active agents

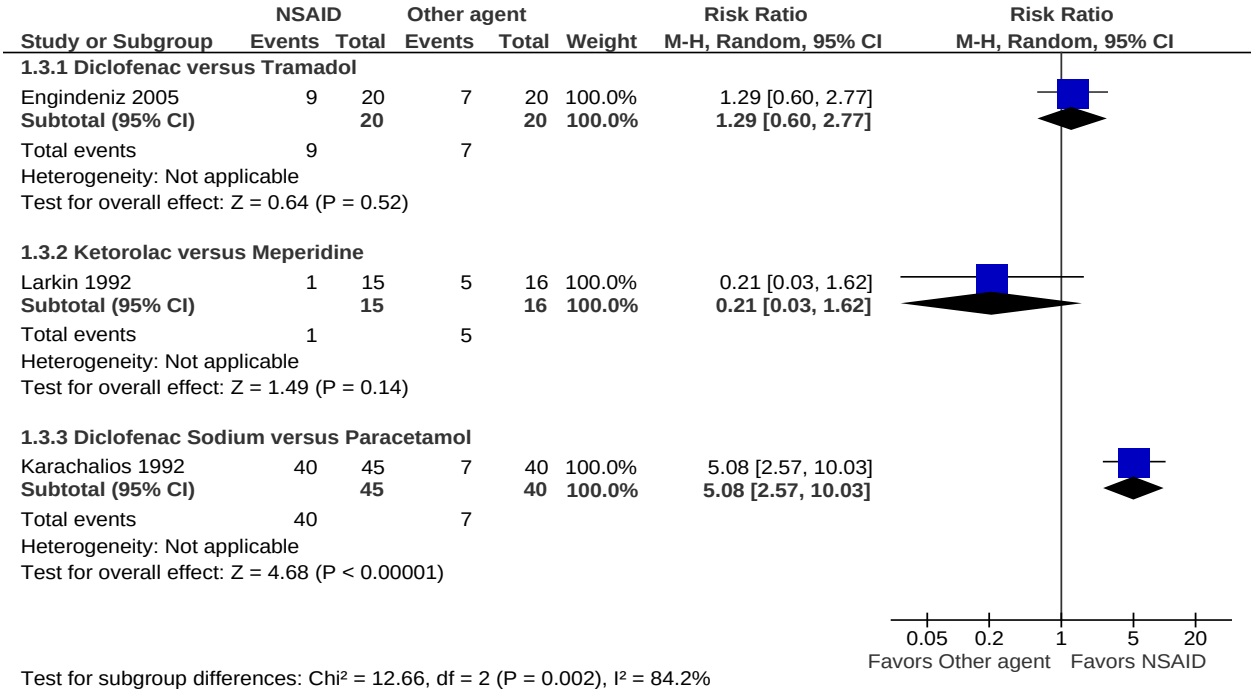
Comparison	Study, Year Study Design (# Patients)	Interventions	Risk of Bias	Outcomes	Data Source
NSAIDs vs. neuroleptics	Seim, 1998 RCT (n = 64)	Prochlorperazine vs. ketorolac	Unclear	Pain intensity–VAS: (MD = -19.00 (95% CI: -34.97, -3.03); favors prochlorperazine	Figure 11
	Shrestha, 1996 RCT (n = 30)	Chlorpromazine hydrochloride vs. ketorolac tropethamine	Low	Pain intensity–VAS: (MD = -5.30 (95% CI: -24.89, 14.29); no significant difference between groups	Figure 11

CI = confidence interval; MD = mean difference; N = number; NSAID = nonsteroidal anti-inflammatory drug; VAS = visual analogue scale

Pain Free at 1-2 Hours

Three studies reported being pain free at 1–2 hours (Figure 20).[81,101,111] One study[111] showed a significant difference in favor of NSAIDs when comparing diclofenac sodium and paracetamol (RR = 5.08; 95% CI: 2.57, 10.03). There was no statistically significant difference in the other two studies.[81,101] One study[81] 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 20. Pain free at 1–2 hours in trials comparing NSAIDs and other active agents



Headache Recurrence at 48 Hours

One study[81] 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[94] 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[101] reported disability at 1 hour and found no difference between ketorolac and meperidine (RR = 0.64; 95% CI: 0.31, 1.32).

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	
Ketorolac vs. meperidine + promethazine	Change in pain–VAS (1; 42)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Pain response (1; 42)	Moderate	Unknown	Direct	Imprecise	Insufficient
Ketorolac vs. meperidine + hydroxyzine	Change in pain–VAS (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Required additional analgesia (1; 50)	Moderate	Unknown	Direct	Imprecise	Insufficient
Ketorolac vs. meperidine	Pain response (1; 31)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Pain free (1-2 hrs) (1; 31)	Moderate	Unknown	Direct	Imprecise	Insufficient
Ketorolac vs. sumatriptan	Change in pain–VAS (1; 29)	Moderate	Unknown	Direct	Precise	Insufficient

Table 12. Strength of evidence for NSAIDs versus active agents (continued)

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Prochlorperazine vs. ketorolac	Change in pain–VAS (1; 64)	Moderate	Unknown	Direct	Precise	Insufficient
Chlorpromazine hydrochloride vs. ketorolac tropethamine	Change in pain–VAS (1; 30)	Low	Unknown	Direct	Imprecise	Insufficient
Lysine acetylsalicylic acid vs. ergotamine	Pain response (1; 112)	Moderate	Unknown	Direct	Precise	Insufficient
Diclofenac vs. tramadol	Pain response (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Pain free (1-2 hrs) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
	Headache recurrence (48 hrs) (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
Diclofenac sodium vs. paracetemol	Pain free (1-2 hrs) (1; 85)	Moderate	Unknown	Direct	Precise	Insufficient

N = number; NRS = numerical rating scale; ROB = risk of bias; VAS = visual analogue scale

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

Comparison	Author, Year, Country, Study Design	Timepoint 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[42]	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[100]	120 min, (2 hr)	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[55]	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[94]	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[81]	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, associated symptoms, rescue treatment, recurrence, adverse events
	Karachalios, 1992, Greece, RCT[111]	180 min, (2-4 hr)	G1: Diclofenac sodium, n=46, 75mg IM G2: Paracetamol, n=40, 500 mg IM	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

Table 13. Patient and study characteristics of trials comparing NSAIDs with placebo or active agent (continued)

Comparison	Author, Year, Country, Study Design	Timepoint 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 active agents	Larkin, 1992, U.S., RCT[101]	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[56]	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[84]	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; 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 receiving placebo based on three RCTs (moderate strength of evidence).
- For all head to head comparisons, single trials compared opioids with other active agents for pain intensity, pain free, and headache recurrence (insufficient strength of evidence).

Results

The results for studies that assessed the effectiveness of opioids are summarized below. Table 14, Table 15, and Table 16 provide results or strength of evidence grades for all key outcomes. See Table 17 for details on study and patient characteristics.

Opioids Versus Placebo

Description of Included Studies

Three RCTs assessed the effectiveness of opioids versus placebo in patients with acute migraine headache.[77,98,113] One study was a four-arm trial that compared nalbuphine monotherapy, nalbuphine plus hydroxyzine, hydroxyzine monotherapy, and placebo. The opioids included pethidine,[113] nalbuphine,[98] nalbuphine plus hydroxyzine,[98] and tramadol.[77] All studies were performed in the ED. The mean age of patient groups ranged from 37 to 40 years. The participants were predominantly female. None of the studies reported the race or ethnicity 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 4 hours to 7 days after ED discharge. Secondary outcomes included headache recurrence and adverse effects.

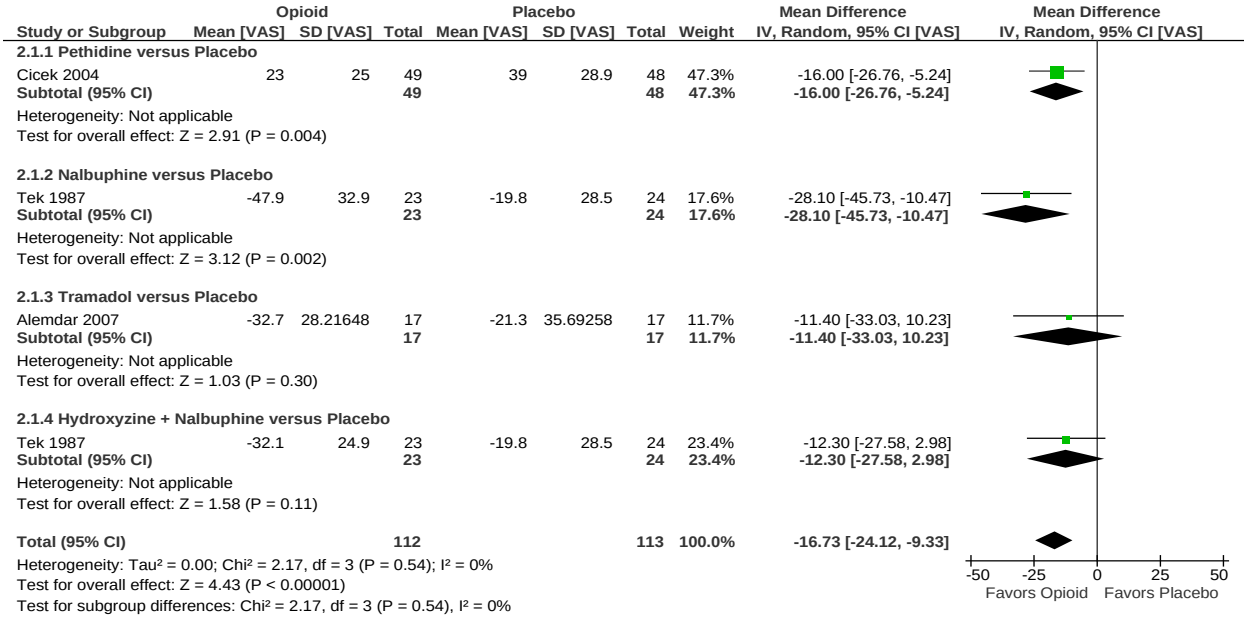
One study[98] had a low risk of bias, one[113] had an unclear risk of bias, and one[77] had a high risk of bias (Appendix D).

Effectiveness Results

Change in Pain Intensity (VAS)

All three studies assessed pain intensity using the VAS (mm) (Figure 21). 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 21. Pain intensity (VAS) in trials comparing opioids and placebo



VAS = visual analogue scale

Pain Free Response

One study[77] 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

Thirteen RCTs assessed the effectiveness of opioids versus other active agents. The opioids included meperidine,[55,94,101] pethidine,[113] tramadol,[81] nalbuphine,[98] meperidine plus dimenhydrinate,[66,112] nalbuphine plus hydroxyzine,[98] butorphanol,[110] and morphine.[115] The other active agents included nalbuphine plus hydroxyzine,[98] hydroxyzine,[98] meperidine plus hydroxyzine,[110] methotrimeprazine,[112] metoclopramide, methotrimeprazine, droperidol, chlorpromazine ketorolac, ketorolac plus promethazine, and DHE. Nine studies [53,55,66,67,81,85,94,101,113] have been described in other sections of the report (metoclopramide, 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 age of intervention groups ranged from 29 to 46 years. See the following tables for details on study and patient characteristics: Table 6 (metoclopramide), Table 9 (neuroleptics), Table 13 (NSAIDs), Table 17 (opioids), and Table 19 (DHE).

Four studies had low risk of bias,[53,66,81,98] seven studies[55,67,85,94,101,113,115] had unclear risk of bias, and two studies[110,112] had a high risk of bias (Appendix D).

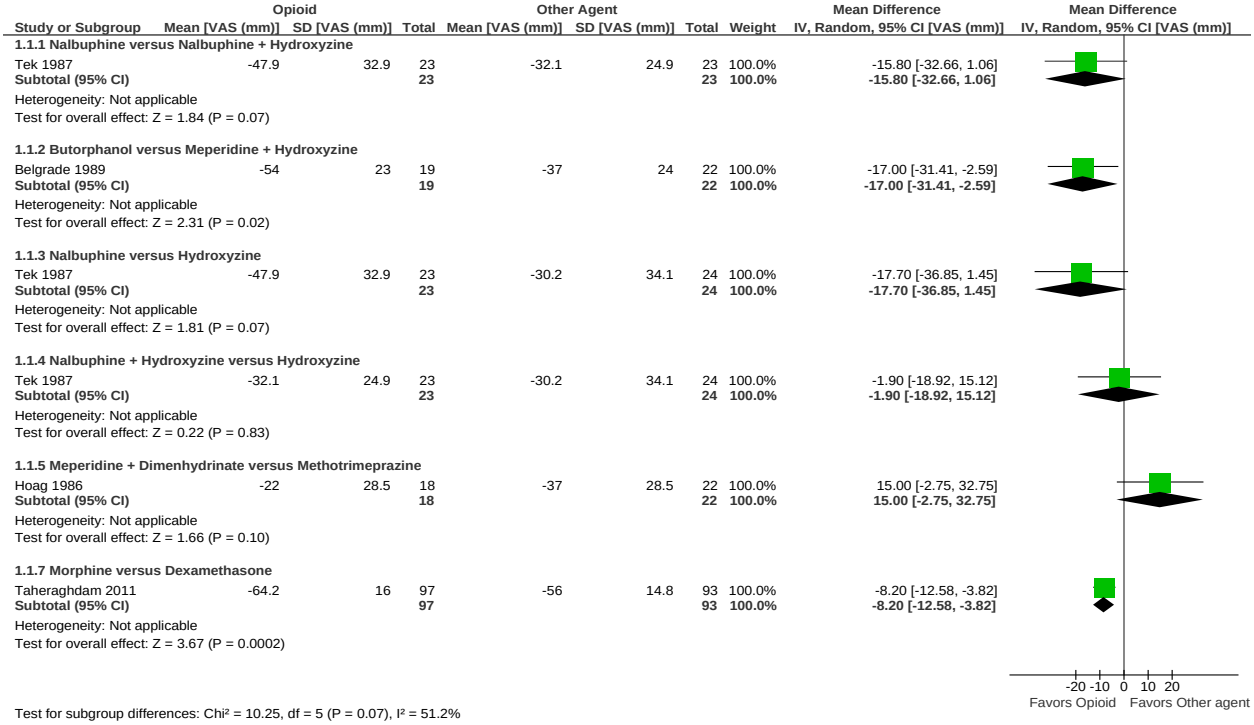
Effectiveness Results

Change in Pain Intensity (VAS)

The four studies[98,110,112,115] that have not been reported in other sections of the report used the VAS (mm) to measure pain intensity (Figure 22). Two studies[110,115] showed a significant result in favor of opioids when comparing butorphanol versus meperidine plus hydroxyzine and morphine versus dexamethasone (MD = -17.00; 95% CI: -31.41, -2.59 and MD = -8.2; 95% CI: -12.58, -3.82 respectively). There was no statistically significant difference between opioids and other active agents in the other two studies. The studies that assessed pain intensity in other sections of the report are summarized in Table 15.

One study measured pain intensity (VAS) at 24 hours[115] and found no statistically significant difference between patients who received morphine and those who received dexamethasone (MD = 1.30, 95% CI: -2.47, 5.07).

Figure 22. Pain intensity (VAS) in trials comparing opioids and other active agents



VAS = visual analogue scale

Pain Free Response

Three studies[55,81,101] reported "pain free after treatment" and found no difference between opioids and other active agents. One trial[81] 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 summarized in Table 15.

Headache Recurrence

One study[81] reported the recurrence of headache at 2 days following the intervention and found no difference between diclofenac and tramadol (RR = 1.50; 95% CI: 0.28, 8.04). The study that assessed headache recurrence previously in another section of the report is summarized in Table 15.

Table 15. Opioids versus active agents in acute migraine

Comparison	Study, Year Study Design (# Patients)	Interventions	Risk of Bias	Outcomes	Data Source
Metoclopramide vs. opioids	Cicek, 2004, RCT (n = 99)	Metoclopramide vs. pethidine	Unclear	Pain intensity–VAS: (MD = -10.00; 95% CI: -19.21, -0.79); favors metoclopramide	Figure 7
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)	Figure 22
	Lane, 1989, RCT (n=46)	Chlorpromazine vs. meperidine + dimenhydrinate	Unclear	Pain intensity–VAS: (MD = -26.10; 95% CI: -40.10, -12.10); favors chlorpromazine	Figure 11
	Richman, 2002, RCT (n=28)	Droperidol vs. meperidine	Unclear	Pain intensity–VAS: (MD = -10.00; 95% CI: -30.03, 10.03);	Figure 11
	Stiell, 1991, RCT (n=74)	Methotrimeprazine vs. meperidine + dimenhydrinate	Low	Pain intensity–VAS: (MD = 6.30; 95% CI: -4.77, 17.37)	Figure 11
Opioids vs. NSAIDs	Davis, 1995, RCT (n=42)	Ketorolac vs. meperidine + promethazine	Unclear	Pain intensity–VAS: (MD = 0.00; 95% CI: -7.51, 7.51) Pain response (post tx): (RR = 0.81; 95% CI: 0.49, 1.31)	Figure 18 Figure 19
	Duarte, 1992, RCT (n=50)	Ketorolac vs. meperidine + hydroxyzine	Unclear	Pain intensity–VAS: (MD = 5.20; 95% CI: -10.08, 20.48)	Figure 18
	Engindinez, 2005, RCT (n=40)	Diclofenac vs. tramadol	Low	Pain response (post tx): (RR = 1.00; 95% CI: 0.73, 1.36); Pain free (1-2hr): (RR = 1.29; 95% CI: 0.60, 2.77) Headache recurrence (48hr): (RR = 1.50; 95% CI: 0.28, 8.04)	Figure 19 Figure 20
	Larkin, 1992, RCT (n=31)	Ketorolac vs. meperidine	Unclear	Pain response (post tx): (RR = 0.53; 95% CI: 0.24, 1.20) Pain free (1-2hr): (RR = 0.21; 95% CI: 0.03, 1.62)	Figure 19 Figure 20

Table 15. Opioids versus active agents in acute migraine (continued)

	Study, Year Study Design (# Patients)	Interventions	Risk of Bias	Outcomes	Data Source
Opioids vs. DHE	Carleton,1988, RCT (n=156)	DHE vs. meperidine	Low	Pain intensity–VAS: (MD = 2.20; 95% CI: -10.03, 14.43);	Figure 23
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 22
	Tek, 1987, RCT (n = 46)	Nalbuphine vs. nalbuphine + hydroxyzine	Low	Pain intensity–VAS: (MD = -15.80; 95% CI: -32.66, 1.06);	Figure 22
Opioids vs. corticosteroid	Taheraghdam, 2011, RCT (n = 190)	Morphine vs. dexamethasone	Unclear	Pain intensity–VAS: (MD = -8.20; 95% CI: -12.58, -3.82); favors morphine	Figure 22

CI = confidence interval; DHE = dihydroergotamine; RR = risk ratio; RCT = randomized controlled trial; Tx = treatement; VAS = visual analogue 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	
Nalbuphine vs. nalbuphine + hydroxyzine	Pain intensity–VAS (1; 46)	Low	Unknown	Direct	Imprecise	Insufficient
Butorphanol vs meperidine + hydroxyzine	Pain intensity–VAS (1; 41)	High	Unknown	Direct	Precise	Insufficient
Nalbuphine vs hydoxyzine	Pain intensity–VAS 1; 47)	Low	Unknown	Direct	imprecise	Insufficient
Nalbuphine + hydroxyzine vs hydroxyzine	Pain intensity–VAS (1;47)	Low	Unknown	Direct	Imprecise	Insufficient
Meperidine + dimenhydrinate vs methotri-meprazine	Pain intensity–VAS (1;40)	High	Unknown	Direct	Imprecise	Insufficient
Morphine vs dexamethasone	Pain intensity–VAS (1; 190)	Moderate	Unknown	Direct	Precise	Insufficient
Diclofenac vs. tramadol	Headache recurrence (48 hrs)	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 with placebo or active agents

Comparison	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[77]	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[113]	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[98]	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)

Table 17. Patient and study characteristics of trials comparing opioids with placebo or active agents (continued)

Comparison	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 active agents	Belgrade, 1989, U.S. RCT[110]	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 (1 to 100 where 100 is worst possible pain) 2: blood pressure
	Hoag, 1986, Canada RCT[112]	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
	Taheraghdam, 2011, Iran RCT[115]	60 min, (24 hr)	G1: Morphine, n=97 , 0.1mg/kg IV G2: Dexamethasone, n=93, 8 mg IV	G1: 42.3 (16.2), 65 (67%), NR G2: 45.93 (16.1), 52 (55.9%), NR	G1: VAS: 8.75 (1.43), NR G2: VAS: 8.49 (1.5), NR	1: pain severity (VAS)
	Tek, 1987, U.S. RCT[98]	60 min, (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; 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

- For all head to head comparisons, single trials compared DHE with other active agents for pain intensity, headache relief, pain response, and headache recurrence (insufficient strength of evidence).

Results

The results for studies that assessed DHE are summarized below. Table 18 provides the strength of evidence grades for all key outcomes. See Table 19 for details on study and patient characteristics.

DHE Versus Active Agents

Description of Included Studies

Five RCTs,[53,56,61,93,96] with six comparisons, assessed the effectiveness of DHE versus other active agents. Active agents included meperidine,[53] diclofenac,[93] sumatriptan,[61] chlorpromazine,[96] lidocaine,[96] and lysine acetylsalicylic acid.[56] One study[56] was described in a previous section (NSAIDs) of this report (Table 13).

Three studies[53,56,96] were conducted in the ED, and two[61,93] were conducted in clinics that managed patients with acute headaches. 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 age of intervention groups ranged from 32 to 42 years. All studies had a pain related primary outcome. Secondary outcomes included adverse effects, functional impairment, recurrence, vital signs, and physician global rating.

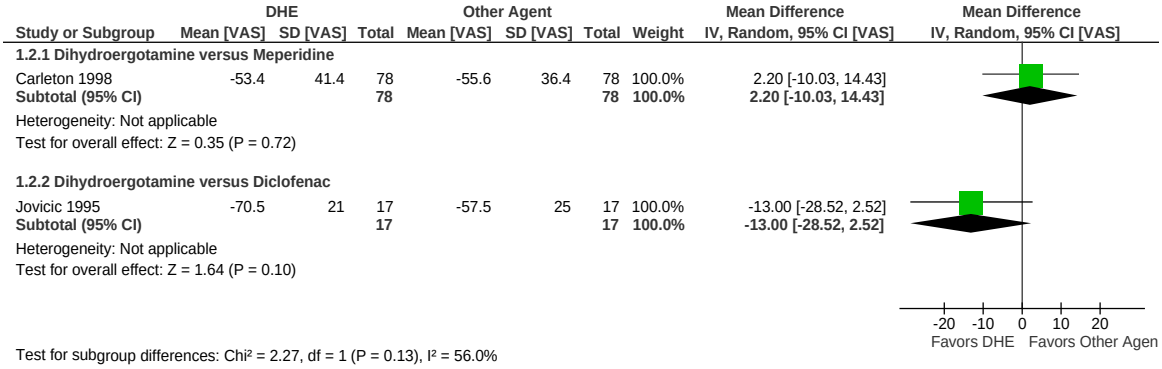
One study[53] had a low risk of bias, three had an unclear risk of bias,[56,61,93] and one[96] had a high risk of bias (Appendix D).

Effectiveness Results

Change in Pain Intensity (VAS)

Change in pain intensity was reported in two studies at 30 minutes[53] and 60 minutes.[53,93] There was no statistically significant difference between DHE and meperidine at 30 minutes,[53] nor was there a difference at 60 minutes between DHE versus diclofenac or DHE versus meperidine (Figure 23).

Figure 23. Pain intensity (VAS) at 60 minutes in trials comparing DHE and other active agents



VAS = visual analogue scale

Headache Relief

Headache relief was reported at 1, 2, 3, 4, and 24 hours in one study.[61] At both 1 and 2 hours, sumatriptan was significantly 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 the 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[56] comparing lysine acetylsalicylic acid and ergotamine showed a statistically significant difference that favored NSAIDs (RR = 1.92; 95% CI: 1.10, 3.36) (Figure 19).

Improvement of Functional Impairment

Two studies[53,61] assessed improvement of functional impairment. One study[53] found that patients receiving DHE had greater functional improvement compared with patients receiving meperidine (RR = 2.27; 95% CI: 1.20, 4.29). The second study[61] found that patients receiving sumatriptan had greater functional improvement compared with patients receiving DHE (RR = 0.65; 95% CI: 0.53, 0.80).

Headache Recurrence

One study reported headache recurrence and found a statistically significant difference in favor of DHE versus sumatriptan (RR = 0.39; 95% CI: 0.26, 0.59).[61]

Nausea and Vomiting

Two studies reported nausea, and one reported vomiting. One study[61] 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 statistically significant difference when comparing DHE with meperidine (RR = 0.94; 95% CI: 0.66, 1.35).[53] One study[61] compared DHE versus sumatriptan for emesis and found no statistically significant 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 Meperidine	Pain intensity–VAS (1; 156)	Low	Unknown	Direct	Imprecise	Insufficient
DHE vs Diclofenac	Pain intensity–VAS (1; 46)	Moderate	Unknown	Direct	Imprecise	Insufficient
DHE vs Sumatriptan	Headache relief (1hr) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief (2 hrs) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief (3 hrs) (1; 295)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief (4 hrs) (1; 295)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief (24 hrs) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache recurrence (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
Lysine acetyl-salicylic acid vs. DHE	Pain response (1; 112)	Moderate	Unknown	Direct	Precise	Insufficient

DHE = dihydroergotamine; 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[53]	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[93] (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[96]	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[61]	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: % 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 60 minutes compared with those receiving placebo based on four RCTs (moderate strength of evidence).
- More patients who received sumatriptan were pain free at discharge compared with those receiving placebo based on five 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).
- For all head to head comparisons, single trials compared sumatriptan with other active agents for change in pain (VAS), headache relief, and headache recurrence (insufficient strength of evidence).

Results

The results for studies comparing triptans and placebo and active comparators are summarized below. Table 20, Table 21, and Table 22 present results or the strength of evidence grades for all key outcomes. See Table 23 for details on study and patient characteristics.

Triptans Versus Placebo

Description of Included Studies

Eight RCTs (in seven publications) compared the effectiveness of triptans versus placebo in the treatment of acute migraine.[57-60,62,106,116] Most studies were conducted in the ED; one study was conducted in neurology departments, pain clinics, and physicians' offices.[116] One publication reported the results of two separate trials;[58] in all metagraphs and analyses these individual trials are labeled as Mushet (1) and Mushet (2). All of the triptans were administered subcutaneously. Six studies evaluated sumatriptan (4-6 mg) and one evaluated almotriptan (2-10 mg).[62]

Most participants were female. The mean age ranged from 38 and 41 years. Two studies reported the ethnicity of participants.[57,58] Six studies evaluated participants at 120 minutes, while in one study patients were assessed at discharge.[106] For one study,[116] we extracted data for the 60 minute timepoint. In this study patients who still had headache at 60 minutes were randomized to receive either placebo or additional medication. Followup timepoints ranged from 12 hours to 5 days; patients were not contacted following discharge in one study.[60] All studies had primary outcomes that were related to pain. Secondary outcomes included nausea, vomiting, disability level, mean duration of migraine attack, headache improvement, functional disability, and headache recurrence.

All RCTs had an unclear risk of bias (Appendix D).[57-60,62,106,116]

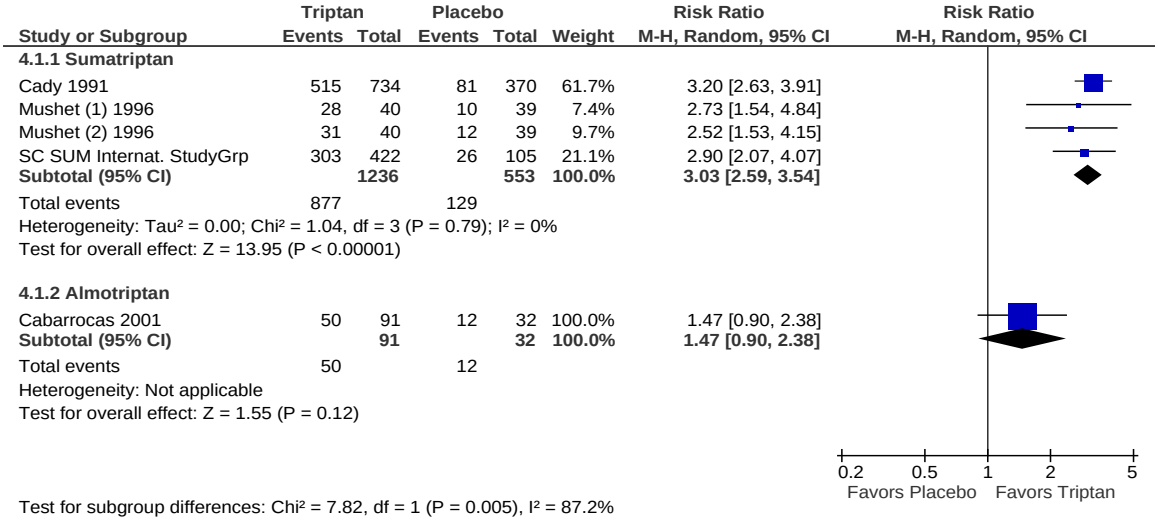
Effectiveness Results

Headache Relief at 60 Minutes

Five trials reported the number of patients who experienced headache relief at 60 minutes (Figure 24).[58,60,62,116] In the four trials involving sumatriptan, the pooled results demonstrated that significantly more patients who received sumatriptan achieved headache relief than those who

received placebo (RR = 3.03; 95% CI: 2.59, 3.54, I^2 = 0%). There was no statistically significant difference between patients who received almotriptan and those who received placebo.[62]

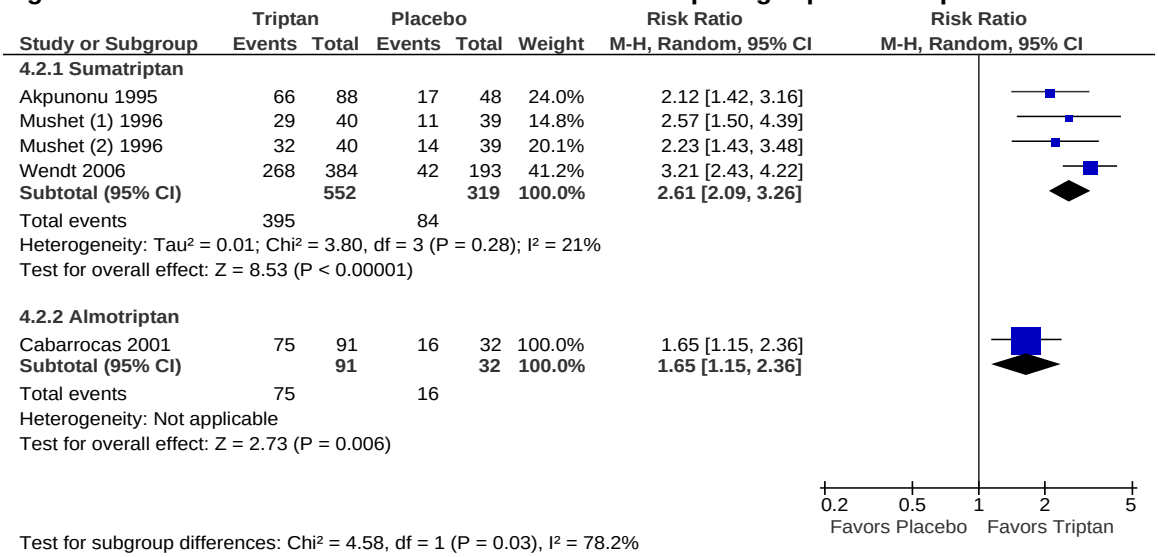
Figure 24. Headache relief at 60 minutes in trials comparing triptans and placebo



Headache Relief at 120 Minutes

There were five comparisons that evaluated the number of patients who experienced headache relief at 120 minutes (Figure 25).[57,58,62,106] The differences between the triptan and placebo groups were statistically significant for sumatriptan (RR = 2.61; 95% CI: 2.09, 3.26; I^2 = 21%) and almotriptan (RR = 1.65; 95% CI: 1.15, 2.36).

Figure 25. Headache relief at 120 minutes in trials comparing triptans and placebo



Headache Relief

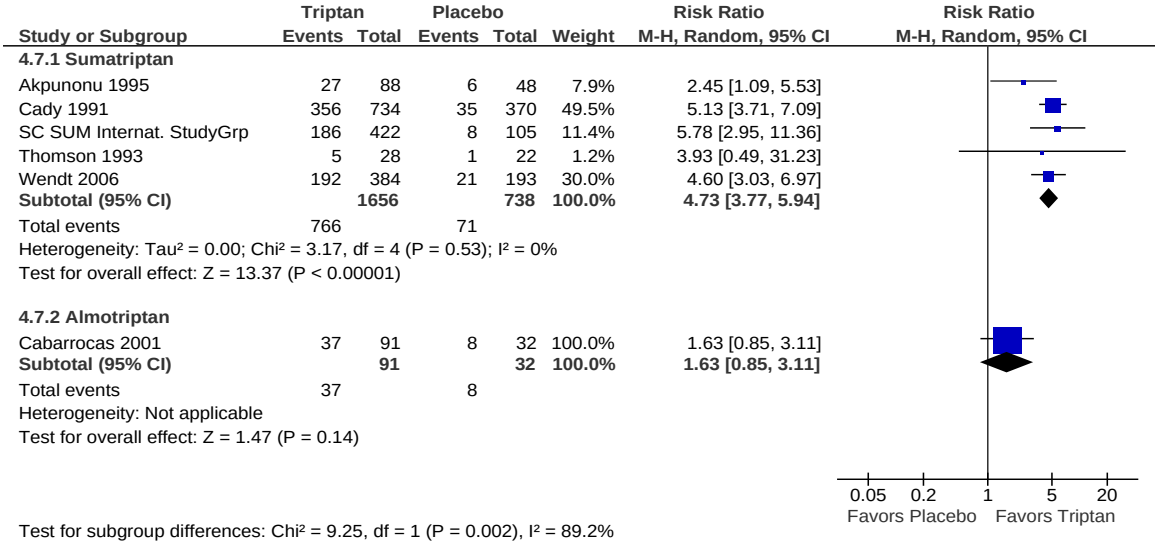
One study measured headache relief on the VAS (mm) at 30, 60, and 120 minutes.[57] A second study measured headache relief at 30 minutes. [59] Patients receiving triptans experienced more relief compared with those receiving placebo. The differences were statistically significant at all timepoints, and the differences increased at each timepoint: 30 minutes—MD = -15.45;

95% CI: -19.49, -11.41(I^2 = 0%), 60 minutes—MD = -25.0; 95% CI: -29.32, -20.68, and 120 minutes—MD = -30.70; 95% CI: -35.02, -26.38.

Pain Free

Six studies measured pain free status at discharge,[106] and at 30,[59] 60,[57,60,62,116] and 120 minutes.[57,60,62] In the studies that compared sumatriptan and placebo,[57,59,60,106,116] the pooled results showed a statistically significant difference in favor of sumatriptan (RR = 4.73; 95% CI: 3.77, 5.94, I^2 = 0%). In the study comparing almotriptan with placebo, there was no statistically significant difference between groups. (Figure 26).

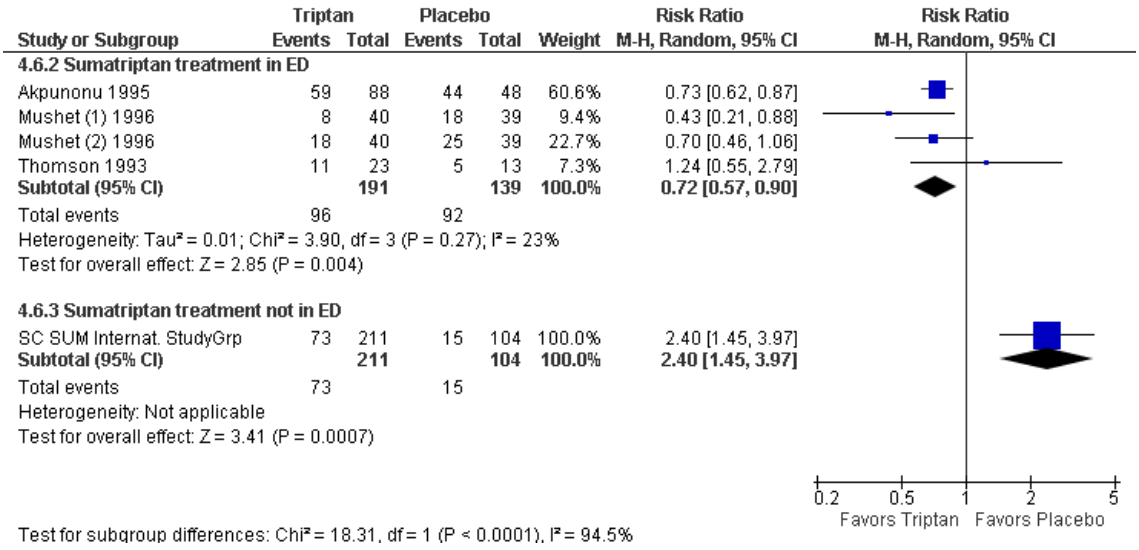
Figure 26. Pain free status in trials comparing triptans and placebo



Headache Recurrence

In five comparisons, patients were contacted within 24 hours of discharge to assess recurrence of migraine headache (Figure 27).[58,59,106,116] The results were inconsistent across comparisons. A subgroup analysis by study setting (i.e., ED vs. other settings[116]) reduced the heterogeneity. The four studies that took place in the ED showed statistically significant results in favor of sumatriptan (RR = 0.72; 95% CI: 0.57, 0.90) while the study that took place in neurology departments, pain clinics, and physicians' offices showed a significant effect in favor of placebo (RR = 2.40; 95% CI: 1.45, 3.97).

Figure 27. Headache recurrence at 24 hours in trials comparing triptans and placebo



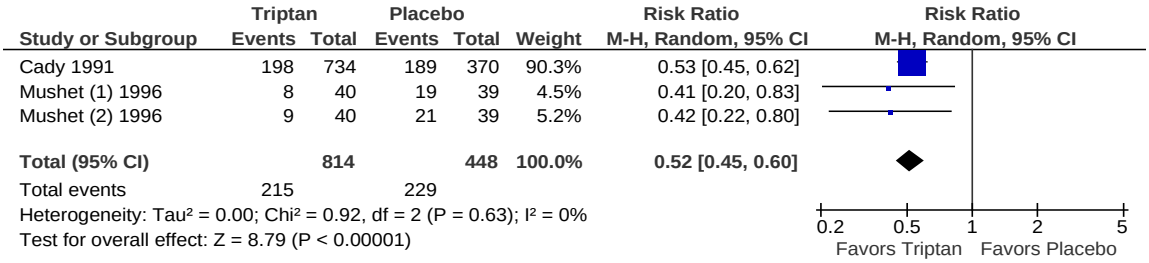
Functional Disability

One study measured functional disability 60 minutes after injection of sumatripan or placebo.[116] Significantly more patients who received sumatriptan experienced an improvement in their ability to function compared with those who received placebo (RR = 5.11; 95% CI: 2.69, 9.70).

Nausea

Three comparisons assessed the effectiveness of sumatriptan in decreasing nausea at 60 minutes (Figure 28).[58,60] The pooled results demonstrated that sumatriptan significantly decreased nausea (RR = 0.52; 95% CI: 0.45, 0.60; I^2 = 0%).

Figure 28. Nausea at 60 minutes in trials comparing triptans and placebo



Vomiting

Two trials[58] assessed vomiting after the administration of sumatriptan versus placebo and found no statistically significant difference between groups (RR = 0.33; 95% CI: 0.03, 3.06; I^2 = 0%).

Photophobia

Three trials examined the effect of sumatriptan versus placebo on photophobia.[58,60] 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%).

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%).[58,60]

Clinical Disability

Two trials compared clinical disability rates between the sumatriptan and placebo groups at 120 minutes.[58] 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.[106] 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.[62] For both outcomes, the differences between groups were not statistically significant.

Patient satisfaction with medication was assessed in two studies[58] 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 (5; 1,789)	Moderate	Consistent	Direct	Precise	Moderate
Almotriptan vs placebo	Headache relief at 60 min (1; 123)	Moderate	Unknown	Direct	Imprecise	Insufficient
Sumatriptan vs placebo	Headache relief at 120 min (4; 1,177)	Moderate	Consistent	Direct	Precise	Moderate
Almotriptan vs placebo	Headache relief at 120 min (1; 123)	Moderate	Unknown	Direct	Precise	Insufficient
Sumatriptan vs placebo	Headache relief–VAS at 30 min (2; 628)	Moderate	Consistent	Direct	Precise	Moderate
	Headache relief–VAS at 60 min (1; 577)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief–VAS at 120 min (1; 577)	Moderate	Unknown	Direct	Precise	Insufficient
Sumatriptan vs placebo	Pain free status (5; 2,394)	Moderate	Consistent	Direct	Precise	Moderate
Almotriptan vs placebo	Pain free status (1; 123)	Moderate	Unknown	Direct	Imprecise	Insufficient
Sumatriptan vs placebo	Headache recurrence–ED setting (4; 330)	Moderate	Inconsistent	Direct	Precise	Low
	Headache recurrence–non-ED setting (1; 315)	Moderate	Unknown	Direct	Precise	Insufficient
Sumatriptan vs placebo	Headache severity at discharge (1; 136)	Moderate	Unknown	Direct	Precise	Insufficient

ED = emergency department; 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,[64] metoclopramide,[82] chlorpromazine and metoclopramide,[32] trimethobenzamide and diphenhydramine,[79] DHE,[61] and ketorolac.[84] These studies are described in other sections of the report (i.e., metoclopramide, neuroleptics, NSAIDs, DHE).

The interventions took place in the ED in all but one study.[61] Outcomes were assessed in the ED between 60 and 120 minutes; the post-ED followup, if applicable, occurred at 24 hours. The mean age of the participant groups ranged from 28 to 42 years. Refer to the following tables for details on study and patient characteristics: Table 6 (metoclopramide), Table 9 (neuroleptics), Table 13 (NSAIDs), Table 19 (DHE).

Two studies had low risk of bias,[64,79] three had unclear risk of bias,[61,82,84] and one[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 (metoclopramide and trimethobenzamide) found no statistically significant difference. One study comparing a neuroleptic agent and sumatriptan reported a statistically

significant difference in favor of the neuroleptic agent. One study comparing NSAIDs and sumatriptan reported a statistically significant difference in favor of NSAIDs.

Headache Relief

Headache relief was reported at 1, 2, 3, 4, and 24 hours in one study.[61] 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).[61]

Table 21. Triptans vs. other active agents

Other Active Agents	Study, Year Study Design (# Patients)	Interventions	Risk of Bias	Outcomes	Data Source
Metoclopramide vs. triptans	Friedman, 2005 RCT (n = 78)	Metoclopramide vs. sumatriptan	Unclear	Pain intensity–VAS: (MD = -9.00; 95% CI: -20.99, 2.99)	Figure 7
	Friedman, 2006 RCT (n = 40)	TMB + DPH vs. sumatriptan	Low	Pain intensity–VAS: (MD = 17.00; 95% CI: -0.08, 34.08)	Figure 7
Neuroleptics vs. triptans	Kostic, 2010 RCT (n=66)	PCZ + DPH vs. sumatriptan	Low	Pain intensity–VAS: (MD = -23.00; 95% CI: -35.50, 10.50); favors neuroleptic	Figure 11
NSAIDs vs. triptans	Meredith, 2003 RCT (n = 29)	KET vs. sumatriptan	Unclear	Pain intensity–VAS: (MD = -48.53; 95% CI: -65.54, -31.51); favors NSAIDs	Figure 18

CI = confidence interval; CPZ = chlorpromazine; DHE = dihydroergotamine; DPH = diphenhydramine; KET = ketorolac; MD = mean difference; PCZ = prochlorperazine; RCT = randomized controlled trial; TMB = trimethobenzamide; VAS = visual analogue scale

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	
Metoclopramide vs. sumatriptan	Change in pain (<2 hr)–VAS (1; 78)	Moderate	Unknown	Direct	Imprecise	Insufficient
Trimethobenzamine + diphen-hydramine vs. sumatriptan	Change in pain (<2 hr)–VAS (1; 40)	Low	Unknown	Direct	Imprecise	Insufficient
Prochlorperazine + DPH vs. sumatriptan	Change in pain–VAS (1; 66)	Low	Unknown	Direct	Precise	Insufficient
Ketorolac vs. sumatriptan	Change in pain–VAS (1; 29)	Moderate	Unknown	Direct	Precise	Insufficient
Sumatriptan vs. DHE	Headache relief (1hr) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief (2 hr) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache relief (3 hr) (1; 295)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief (4 hr) (1; 295)	Moderate	Unknown	Direct	Imprecise	Insufficient
	Headache relief (24 hr) (1; 295)	Moderate	Unknown	Direct	Precise	Insufficient
	Headache recurrence (1; 270)	Moderate	Unknown	Direct	Precise	Insufficient

DHE = dihydroergotamine; DPH = diphenhydramine; 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 [106]	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 [62]	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 [60]	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 [58]	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)

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

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
Subcutaneous Sumatriptan Study Group, 1991, the Netherlands, RCT[116]	120 min, (24 hr)	G1: SUM, n=423. 6mg SC P: Placebo, n=106,	G1: 41 (11), 344 (81.3), NR P: 39 (11), 88 (80), NR	G1: NR; 425 median (min) P: NR; 357 median (min)	1: headache relief 2: headache improvement, functional disability and headache recurrence.
Thomson, 1993, New Zealand, RCT[59]	120 min, (24 hr)	G1: SUM, n=28, 4mg SC P: Placebo, n=23, 0.5ml SC	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 injection 2: change in nausea, vomiting, photophobia; disability level; rescue medication; recurrence; headache improvement
Wendt, 2006, U.S., RCT [57]	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 painmild: 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 Sulfate

Key Points

- Patients who received $MgSO_4$ had greater improvement in pain intensity as measured by the VAS (mm) compared with those receiving placebo based on three RCTs (moderate strength of evidence).
- There was no difference in headache recurrence for patients who received $MgSO_4$ compared with those receiving placebo based on two RCTs (low strength of evidence).
- For head to head comparisons, single trials compared $MgSO_4$ and other active agents for pain intensity measured by the VAS (insufficient strength of evidence).

Results

The results of the studies that assessed magnesium sulfate ($MgSO_4$) are summarized below. Table 24, Table 25, and Table 26 provide the results and strength of evidence grades for all key outcomes. See Table 27 for details on study and patient characteristics.

Magnesium Sulfate Versus Placebo

Description of Included Studies

Four RCTs[44,72,83,99] assessed the effectiveness of $MgSO_4$ compared with placebo. Two studies[44,72] were conducted in headache clinics, and two[83,99] took place in the ED. The mean age of participant groups ranged from 29 to 40 years. The participants were predominantly female. One study[99] reported that participants were predominantly white. All studies reported pain relief or severity as the primary outcome. Timepoints ranged from 20 to 60 minutes. Post-ED followup was 24 hours. Secondary outcomes included headache response, recurrence, use of rescue medication, and adverse effects.

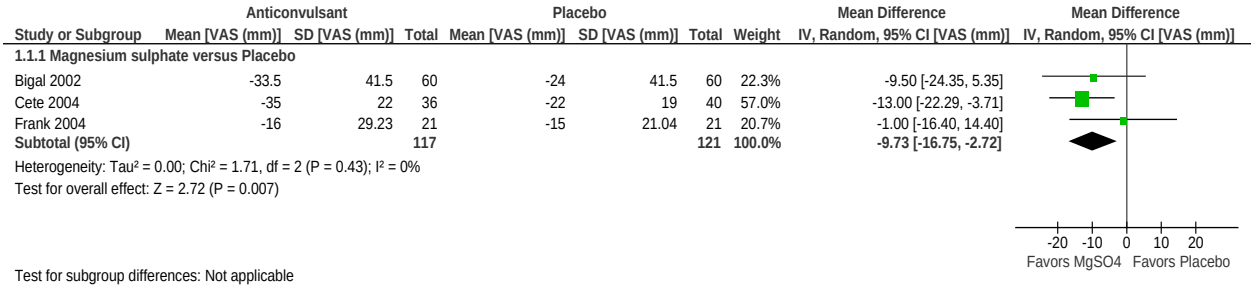
Two studies[83,99] had a low risk of bias and two[44,72] had an unclear risk of bias (Appendix D).

Effectiveness Results

Change in Pain Intensity (VAS)

Three studies reported pain intensity using the VAS (mm) (Figure 29).[44,83,99] The pooled estimate demonstrated a statistically significant difference in favor of $MgSO_4$ (MD = -9.73; 95% CI: -16.75, -2.72; I^2 = 0%).

Figure 29. Pain intensity (VAS) in trials comparing $MgSO_4$ and placebo

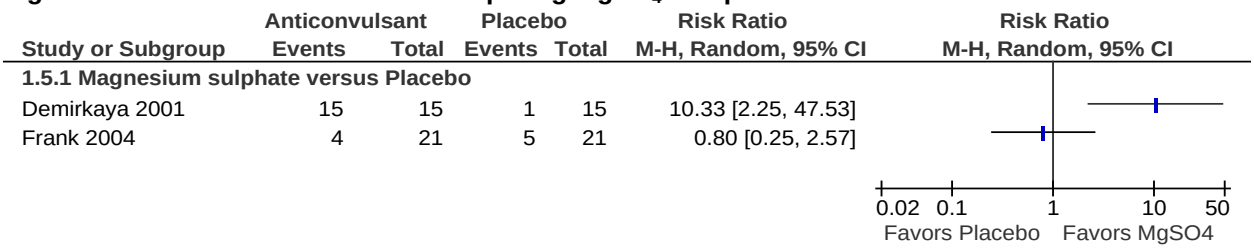


VAS = visual analogue scale

Pain Reduction

Two studies reported pain reduction.[72,99] The results were inconsistent (Figure 30).

Figure 30. Pain reduction in trials comparing $MgSO_4$ and placebo



Headache Recurrence

Two studies[44,83] reported headache recurrence. The pooled results showed no significant difference between $MgSO_4$ and placebo (RR = 0.68; 95% CI: 0.29, 1.63; I^2 = 78%).

Other Outcomes

One study[44] assessed headache response, and use of rescue medications. The results showed significant effect in favor of $MgSO_4$ (RR = 2.78; 95% CI: 1.42, 5.44 and RR = 0.65; 95% CI: 0.53, 0.82, respectively).

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 (3; 238)	Moderate	Consistent	Direct	Precise	Moderate
$MgSO_4$ vs placebo	Pain reduction (2; 72)	Moderate	Inconsistent	Direct	Not pooled	Insufficient
$MgSO_4$ vs placebo	Headache recurrence (2; 196)	Moderate	Consistent	Direct	Imprecise	Low
$MgSO_4$ vs placebo	Headache response at (60 min) (1; 120)	Moderate	Unknown	Direct	Precise	Insufficient

$MgSO_4$ = magnesium sulfate; N = number; ROB = risk of bias; VAS = visual analogue scale

Magnesium Sulfate Versus Active Agents

Description of Included Studies

One study compared the effectiveness of $MgSO_4$ and prochlorperazine[89] and one study compared $MgSO_4$ and metoclopramide.[83] These studies are described in other sections of the report (metoclopramide; neuroleptics).

In both studies the interventions took place in the ED; outcomes were measured at 30 minutes following the intervention. One study[83] also assessed participants at 24 hours post intervention. One study[83] reported a mean age of 40 years. See the following tables for details on study and patient characteristics: Table 6 (metoclopramide), 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 a neuroleptics agent and $MgSO_4$, the results were not statistically significant.

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

Comparison	Study, Year Study Design (# Patients)	Interventions	Risk of Bias	Outcomes	Data Source
Metoclopramide vs. $MgSO_4$	Cete, 2004 RCT (n = 113)	Metoclopramide vs. $MgSO_4$	Low	Pain intensity–VAS: (MD = -5.00; 95% CI: -15.80, 5.80)	Figure 7
Neuroleptic 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 neuroleptic	Figure 11

CI = confidence interval; MD = mean difference; $MgSO_4$ = magnesium sulfate; PCZ = prochlorperazine; RCT = randomized controlled trial; VAS = visual analogue 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	
Metoclopramide vs. $MgSO_4$	Pain intensity–VAS (1; 113)	Low	Unknown	Direct	Imprecise	Insufficient
Prochlorperazine vs. $MgSO_4$	Pain intensity–VAS (1; 36)	Low	Unknown	Direct	Precise	Insufficient

$MgSO_4$ = magnesium sulfate; 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
Bigal, , 2002, Brazil, RCT[44]	60min, (24hr)	G1: $MgSO_4$, n=60, 1 g IV P: Placebo, n=60, NR IV	G1: 29.25, n=45, NR P: 27.6, n=37, NR	G!: NR, 4.4 hr P: NR, 3.65hr	1: pain intensity (10-point VAS) 2: headache response, therapeutic gain, pain recurrence, rescue medication, intensity of adverse events.
Cete, 2004, Turkey, RCT[83]	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 [99]	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 [72]	120 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; IV = intravenous; $MgSO_4$ = magnesium sulfate; 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[98] compared the effectiveness of hydroxyzine and placebo in the treatment of acute migraine headache. The study was conducted in the ED. Headache relief measured at 60 minutes was the primary outcome. Post-ED followup occurred at 7 days. No secondary outcomes were reported (Table 28 and 29). The study had a low risk of bias (Appendix D).

Effectiveness Results

Pain Relief (VAS)

The authors found no statistically significant difference in pain relief comparing hydroxyzine with placebo (MD = 10.40; 95% CI: -7.38, 28.18).[98]

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	Headache relief–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[98]	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

- For all head to head comparisons single trials compared different combination interventions with other active agents for pain relief (insufficient strength of evidence).
- A post hoc mixed treatment analysis found that combination therapy (metoclopramide plus DHE and prochlorperazine plus DHE) and neuroleptic monotherapy were most effective for pain relief (VAS) (low strength of evidence).

Description of Included Studies

Eight RCTs[32,86,102,104,107,108,110,113] assessed the effectiveness of two active interventions versus one or more active interventions (Table 30 and Table 31). None of the trials used the same combination of drugs. The studies were all performed in the ED. The mean age of patient groups ranged from 29 to 43 years. Five trials,[32,86,108,110,113] with six separate interventions, reported pain reduction on the VAS (mm) measured between 30 and 120 minutes post-treatment. Two trials[104,107] reported headache relief as a dichotomous outcome measured at 30 minutes and 4 hours. Risk of bias was unclear for five trials,[86,102,107,108,113] and high for three[32,104,110] (Appendix D).

Effectiveness Results

Three interventions[102,110,113] showed 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 interventions because results were from single trials.

Table 30. Summary of studies reporting active combination therapy versus active therapy for pain reduction (VAS)

Author, Year, Study Design	Intervention	Sample Size	Risk of Bias	Effect Estimate (95% CI)	Strength of Evidence
Belgrade, 1989, RCT[110]	MET+DHE vs. BUT	45	High	MD = -5.00 (-19.98, 9.98)	Insufficient
Belgrade, 1989, RCT[110]	MET+DHE vs. MEP+HDZ	45	High	MD = -22.00 (-36.66, -7.34) favors MET+DHE	Insufficient
Callaham,1986, RCT[108]	PCZ+DHE vs. PCZ	34	Unclear	MD = 5.00 (-18.96, 28.96)	Insufficient
Cicek, 2004, RCT [113]	MET+PET vs. MET	245	Unclear	MD = 0.00 (-8.47, 8.47)	Insufficient
Cicek, 2004, RCT[113]	MET+PET vs. PET	98	Unclear	MD = -10.0 (-19.2, -0.79), favors MET+PET	Insufficient
Corbo, 2001, RCT[86]	MET+$MgSO_4$ vs MET	44	Unclear	MD = 16.00 (-1.58, 33.58)	Insufficient
Edwards, 2001, RCT[104]	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[102]	MET+DHE vs. KET	18	Unclear	MD = -30.0 (-57.72, -2.28); favors MET+DHE]	Insufficient
Klapper, 1989, RCT[107]	MET+DHE vs MET+DEX	20	Unclear	RR = 0.95 (0.61, 1.49)	Insufficient

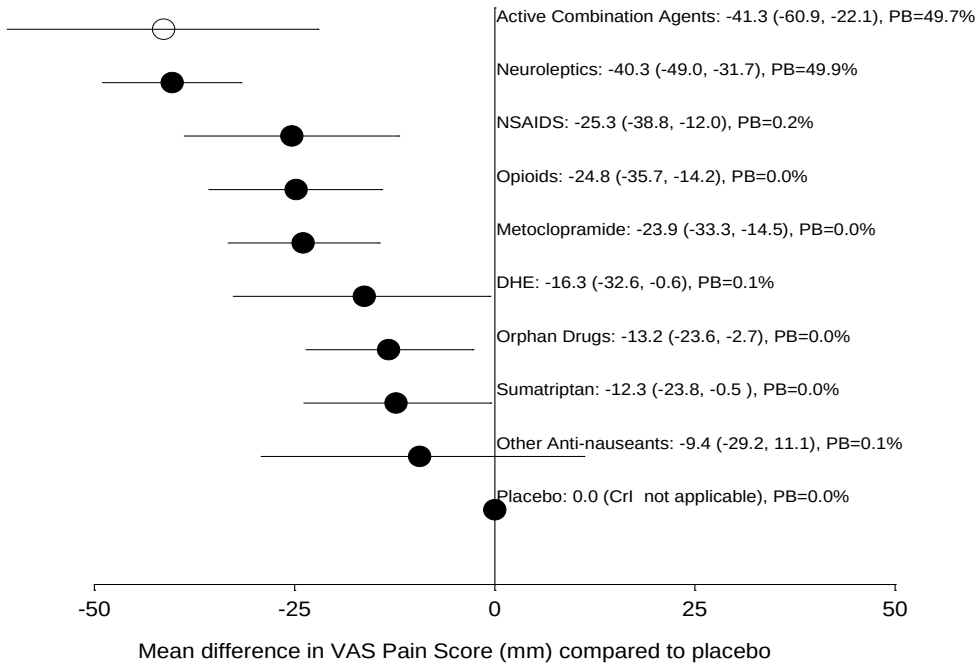
BUT = butorphanol; CPZ = chlorpromazine; DEX = dexamethasone; DHE = dihydroergotamine; ED = emergency department; HDZ = hydroxyzine; KET = ketorolac; MD = mean difference; MEP = meperidine; MET = metoclopramide; $MgSO_4$ = magnesium sulfate; PET = pethidine; PCZ = prochlorperazine; RCT = randomized controlled trial; RR = risk ratio; SUM = sumatriptan; VAL = valproate; VAS = visual analogue scale

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 agents (i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide), we examined active combination therapy. The combination agents were metoclopramide plus DHE[102,110] and prochlorperazine plus DHE.[108] The results showed that both combination therapy and neuroleptic agents were most effective in pain relief, with a pain reduction of approximately 40 mm on the VAS (Figure 31). Metoclopramide, NSAIDs, and opioids reduced pain by approximately 24 mm. There were other, albeit less effective agents (e.g., DHE, triptans, and orphan agents) which reduced pain by approximately 12-16 mm. See Appendix F for the network diagram.

The strength of evidence for the mixed treatment analysis was low. The overall risk of bias for these trials was assessed as moderate and the results were consistent. Since only one or two trials contributed data to some of the network nodes, we downgraded the strength of evidence to low.

Figure 31. Mixed treatment analysis of studies reporting pain score (VAS)



DHE = dihydroergotamine; NSAIDs = nonsteroidal anti-inflammatory drugs; PB = probability; VAS = visual analogue scale

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 [113]	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 [86]	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[108]	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 [110]	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

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

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
Kelly, 1997, Australia and New Zealand, RCT [32]	120 min, (NA)	G1: CPZ, n=23, 12.5 mg IV G2: SUM, n=20, 6 mg IM	G1: 35 (NR), 17 (73.9), NR G2: 32 (NR), 12 (60.0) NR	G1: VAS: 75.7 (95% CI: 68.8, 82.6), NR G2: VAS: 74.6 (95% CI: 67.3, 81.9), NR	1: mean pain scores (VAS)
Klapper, 1989, U.S., RCT [107]	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 [102]	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 [104]	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; IM = intramuscular; IV = intravenous; KET = ketorolac; MEP = meperidine; MET = metoclopramide; $MgSO_4$ = magnesium sulfate; 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.[19-21,76,78,103,109] In every study, all patients were given standard abortive therapy after which they were administered either a placebo or intravenous (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.[103]

All trials were conducted in the ED. The mean age 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,[19,21,78] one assessed patients at 120 minutes after administration of the intervention,[20] and two studies did not assess patients in the ED.[103,109] One study contacted patients at 3 and 30 days post discharge,[76] and another assessed patients at 7 days after discharge.[21] The post-ED followup timepoints for the remaining studies ranged from 24 to 72 hours. See Table 32 and Table 33 for strength of evidence grades and study and patient characteristics, respectively.

Three studies had an unclear risk of bias,[21,76,78,109] and four studies[19,20,78,103] had a low risk of bias (Appendix D).

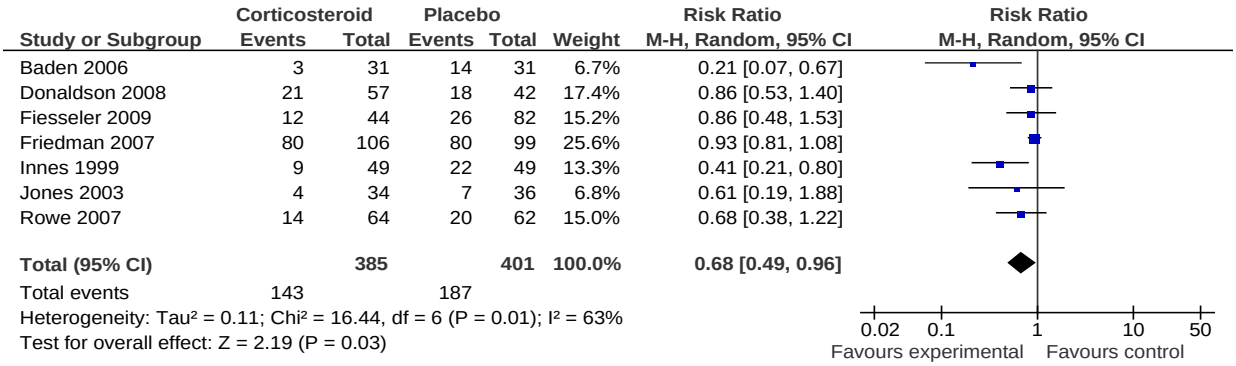
Effectiveness Results

Headache Recurrence (24–72 hours)

We used the authors' definitions of recurrence. In two studies,[19,109] 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 32). 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.,[78] which 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 similar treatment effect (RR = 0.69; 95% CI: 0.40, 1.18; I^2 = 65%) to those using 15 mg or more (RR = 0.65; 95% CI: 0.43 to 0.99; I^2 = 37%). The difference between these two subgroups was not significant ($\chi 2 = 2.01$; df=1; p=0.16).

Figure 32. Recurrence of pain/headache (24-72 hours) in trials comparing dexamethasone and placebo



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 placebo.[78] 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.[21] 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 statistically significant difference between dexamethasone and placebo (RR = 0.90; 95% CI: 0.58, 1.41).[76]

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

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[78]	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[76]	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[103]	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 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[20]	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

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

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
Innes, 1999, Canada, RCT[19]	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[109]	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[21]	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)

DEX = dexamethasone; ED = emergency department; G1 = group 1; IM = intramuscular; IV = intravenous; N = number; 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

- No two studies reported the same adverse effects for the same pair of interventions. The strength of evidence is insufficient to conclude which active treatment for acute migraine results in more or less adverse effects
- Adverse effects were examined for individual arms of the trials and rates of adverse effects reported. Strength of evidence was not graded for these comparisons.
- 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.
- Adverse effects for triptans were infrequently reported; the most common adverse effect was local reactions.
- There were few short-term side effects reported for NSAIDs and opioids.

This section addresses the short-term adverse effects of parenteral pharmacological interventions used to treat acute migraine headaches. Reporting of adverse effects was inconsistent across this body of evidence. As a result, no two studies reported the same adverse effects for the same pair of interventions. The strength of evidence is insufficient to conclude which active treatment for acute migraine results in more or less adverse effects.

As a post hoc analysis we analyzed adverse effects for individual arms of the trials. The results are presented by adverse effect categories (e.g., sedation, dizziness, vomiting). 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.

Nausea or Vomiting

There were 26 unique studies that reported on the rates of vomiting, nausea, and emesis (Figure 33, Table 34).[21,32,43,53,57,58,60,61,63,65-67,75,76,79,81,91,94,98,100,101,104,106,109,110,113] When participants took the placebo, the risk of vomiting or experiencing nausea and emesis was 11 percent (95% CI: 6 to 14 percent). The risk for active agents ranged from 0 percent (95% CI: 0 to 4 percent) to 57 percent (95% CI: 41 to 72 percent).

Figure 33. Risk of nausea or vomiting reported in acute migraine trials

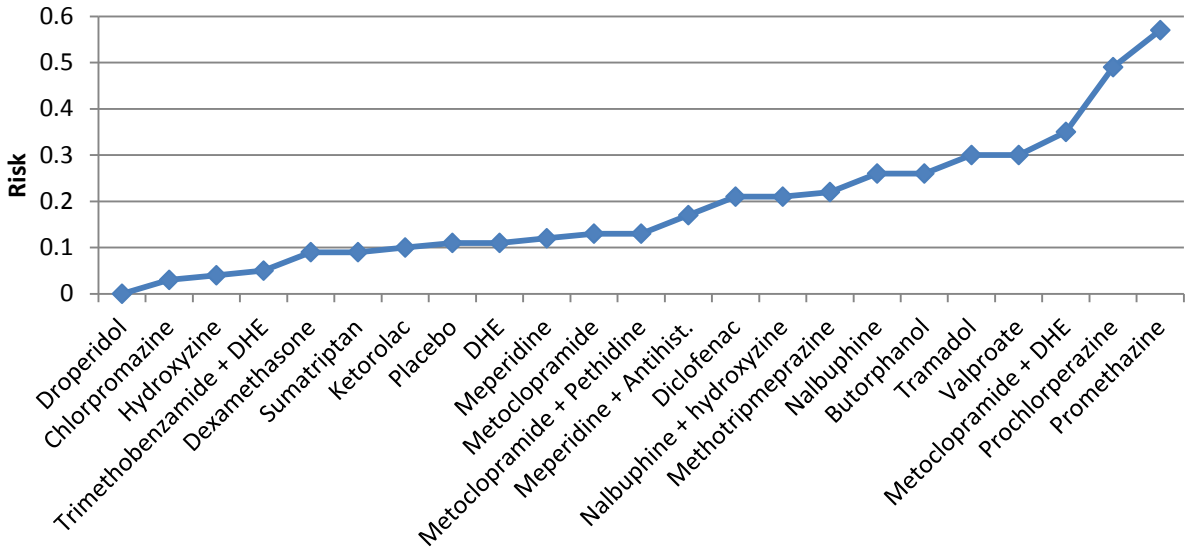


Table 34. Vomiting, nausea, emesis reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Cicek, 2004[113]	5/83	0.06 [0.03, 0.13]
	Tek, 1987[98]	2/24	0.08, 0.02, 0.26]
	Krymchantowski, 2003[100]	1/12	0.08 [0.01, 0.35]
	Wendt, 2006[57]	15/193	0.08 [0.05, 0.12]
	Bigal, 2002[43]	10/30	0.33 [0.17, 0.51]
	Mushet, 1996[58]	11/79	0.14 [0.08, 0.23]
	Cady, 1991[60]	52/370	0.14 [0.11, 0.18]
	Silberstein, 2003[63]	3/61	0.05 [0.02, 0.14]
	Subtotal N=8	99/852	0.11 [0.06, 0.14]
Butorphanol	Belgrade, 1989[110]	5/19	0.26 [0.12, 0.49]
	Subtotal N=1	5/19	0.26 [0.12, 0.49]
Chlorpromazine	Cameron, 1995[65]	1/47	0.02 [0.00, 0.11]
	Lane, 1989[67]	2/24	0.08 [0.02, 0.26]
	Bigal, 2002[43]	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[21]	4/64	0.06 [0.02, 0.15]
	Donaldson, 2008[76]	9/57	0.16 [0.09, 0.27]
	Jones, 2003[109]	2/34	0.06 [0.02, 0.19]
	Subtotal N=3	15/155	0.09 [0.03, 0.14]
DHE	Carleton, 1998[53]	8/85	0.09 [0.05, 0.17]
	Belgrade, 1989[110]	7/21	0.33 [0.17, 0.55]
	Winner, 1996[61]	8/152	0.05 [0.03, 0.10]
	Subtotal N=3	23/258	0.11 [0.02, 0.20]
Diclofenac	Engindeniz, 2005[81]	5/24	0.21 [0.09, 0.40]
	Subtotal N=1	5/24	0.21 [0.09, 0.40]
Droperidol	Silberstein, 2003[63]	0/61	0.00 [0.00, 0.04]
	Subtotal N=1	0/61	0.00 [0.00, 0.04]
Hydroxyzine	Tek, 1987[98]	1/23	0.04 [0.01, 0.21]
	Subtotal N=1	1/23	0.04 [0.01, 0.21]
Ketorolac	Duarte, 1992[94]	3/25	0.12 [0.04, 0.30]
	Larkin, 1992[101]	1/15	0.07 [0.01, 0.30]
	Subtotal N=2	4/40	0.10 [0.00, 0.19]

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

Intervention	Author, Year	n/N	Risk (95% CI)
Meperidine	Carleton, 1998[53]	20/85	0.24 [0.16, 0.34]
	Larkin, 1992[101]	1/16	0.06 [0.01, 0.28]
	Belgrade, 1989[110]	1/22	0.05 [0.01, 0.22]
	Subtotal N=3	22/123	0.12 [0.00, 0.25]
Meperidine plus antihistiamine	Duarte, 1992[94]	4/25	0.16 [0.06, 0.35]
	Lane, 1989[67]	2/22	0.09 [0.03, 0.28]
	Stiell, 1991[66]	10/37	0.27 [0.15, 0.43]
	Subtotal N=3	16/84	0.17 [0.07, 0.28]
Methotrimeprazine	Stiell, 1991[66]	8/37	0.22 [0.11, 0.37]
	Subtotal N=1	8/37	0.22 [0.11, 0.37]
Metoclopramide	Cicek, 2004[113]	6/85	0.07 [0.03, 0.15]
	Jones, 1996[91]	11/29	0.38 [0.23, 0.56]
	Cameron, 1995[65]	1/44	0.02 [0.00, 0.12]
	Subtotal N=3	18/158	0.13 [0.00, 0.25]
Metoclopramide plus pethidine	Cicek, 2004[113]	11/84	0.13 [0.07, 0.22]
	Subtotal N=1	11/84	0.13 [0.07, 0.22]
Metoclopramide plus DHE	Edwards, 2001[104]	7/20	0.35 [0.18, 0.57]
	Subtotal N=1	7/20	0.35 [0.18, 0.57]
Nalbuphine	Tek, 1987[98]	6/23	0.26 [0.13, 0.46]
	Subtotal N=1	6/23	0.26 [0.13, 0.46]
Nalbuphine plus hydroxyzine	Tek, 1987[98]	5/24	0.21 [0.09, 0.40]
	Subtotal N=1	5/24	0.21 [0.09, 0.40]
Prochlorperazine	Callan, 2008[75]	17/35	0.49 [0.33, 0.64]
	Jones, 1996[91]	14/28	0.50 [0.33, 0.67]
	Subtotal N=2	31/63	0.49 [0.38, 0.61]
Promethazine	Callan, 2008[75]	20/35	0.57 [0.41, 0.72]
	Subtotal N=1	20/35	0.57 [0.41, 0.72]
Sumatriptan	Friedman, 2006[79]	6/20	0.30 [0.15, 0.52]
	Kelly, 1997[32]	1/20	0.05 [0.01, 0.24]
	Wendt, 2006[57]	28/384	0.07 [0.05, 0.10]
	Mushet, 1996[58]	10/79	0.13 [0.07, 0.22]
	Akpunonu, 1995[106]	8/88	0.09 [0.05, 0.17]
	Cady, 1991[60]	68/547	0.12 [0.10, 0.15]
	Winner, 1996[61]	6/158	0.04 [0.02, 0.08]
	Subtotal N=7	127/1296	0.09 [0.05, 0.13]
Tramadol	Engindeniz, 2005[81]	7/23	0.30 [0.16, 0.51]
	Subtotal N=1	7/23	0.30 [0.16, 0.51]
Trimethobenzamide plus DHE	Friedman, 2006[79]	1/20	0.05 [0.01, 0.24]
	Subtotal N=1	1/20	0.05 [0.01, 0.24]
Valproate	Edwards, 2001[104]	6/20	0.30 [0.15, 0.52]
	Subtotal N=1	6/20	0.30 [0.15, 0.52]

CI = confidence interval; DHE = dihydroergotamine; N = number

Sedation or Somnolence

There were 25 studies that reported the development of sedation or somnolence including drowsiness and decreased levels of consciousness (Figure 34, Table 35).[19,20,22,43,53,57,60,65-68,75,79,85-87,91,94,97,98,101,109,110,113] The risk of developing sedation or 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 34. Risk of sedation reported in migraine trials

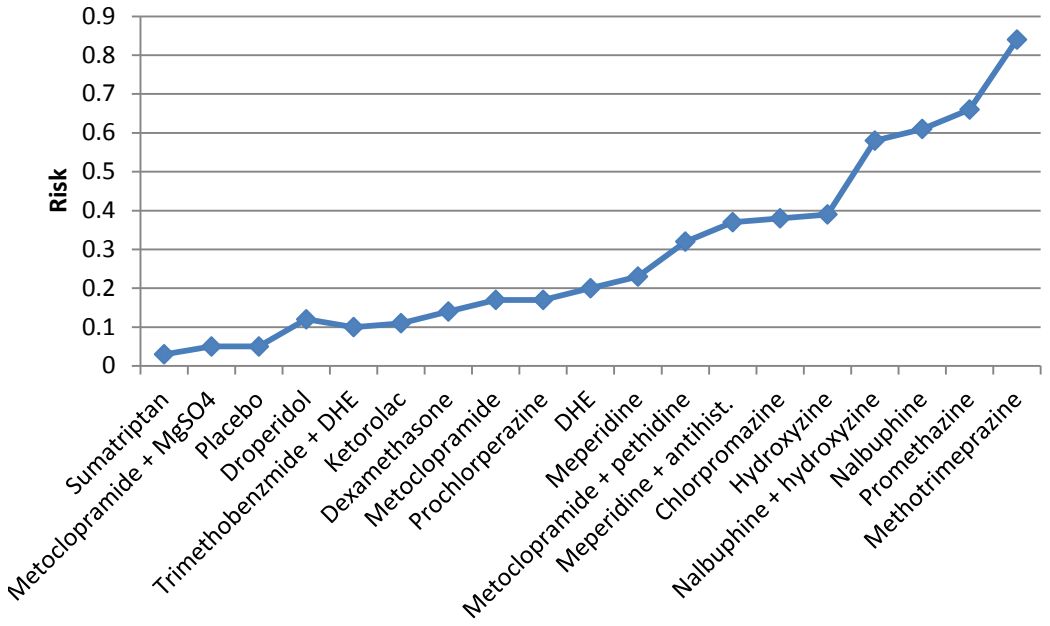


Table 35. Sedation/somnolence reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Cicek, 2004[113]	4/83	0.05 [0.02, 0.12]
	McEwen, 1987[97]	6/17	0.35 [0.17, 0.59]
	Tek, 1987[98]	4/24	0.17 [0.07, 0.36]
	Wendt, 2006[57]	4/193	0.02 [0.01, 0.05]
	Cady, 1991[60]	8/370	0.02 [0.01, 0.04]
	Jones, 2003[109]	4/36	0.11 [0.04, 0.25]
	Silberstein, 2003[63]	5/61	0.08 [0.04, 0.18]
	Subtotal N=7	35/784	0.05 [0.02, 0.09]
Chlorpromazine	Cameron, 1995[65]	8/47	0.17 [0.09, 0.30]
	Lane, 1989[67]	5/24	0.21 [0.09, 0.40]
	McEwen, 1987[97]	15/19	0.79 [0.57, 0.91]
	Subtotal N=3	28/90	0.38 [0.03, 0.74]
Standard abortive therapy plus Dexamethasone	Friedman, 2007[20]	3/106	0.03 [0.01, 0.08]
	Innes, 1999[19]	12/49	0.24 [0.15, 0.38]
	Jones, 2003[109]	6/34	0.18 [0.08, 0.34]
	Subtotal N=3	21/189	0.14 [0.00, 0.29]
DHE	Carleton, 1998[53]	17/85	0.20 [0.13, 0.30]
	Subtotal N=1	17/85	0.20 [0.13, 0.30]
Droperidol	Silberstein, 2003[63]	12/61	
	Richman, 2002[85]	1/15	0.07 [0.01, 0.30]
	Miner, 2001[87]	7/82	0.09 [0.04, 0.17]
	Subtotal N=3	20/158	0.12 [0.04, 0.20]
Hydroxyzine	Tek, 1987[98]	9/23	0.39 [0.22, 0.59]
	Subtotal N=1	9/23	0.39 [0.22, 0.59]
Ketorolac	Duarte, 1992[94]	2/25	0.08 [0.02, 0.25]
	Larkin, 1992[101]	3/15	0.20 [0.07, 0.45]
	Subtotal N=2	5/40	0.11 [0.01, 0.22]

Table 35. Sedation/somnolence reported in acute migraine trials (continued)

Intervention	Author, Year	n/N	Risk (95% CI)
Meperidine	Richman, 2002[85]	2/14	0.14 [0.04, 0.40]
	Carleton, 1998[53]	23/85	0.27 [0.19, 0.37]
	Larkin, 1992[101]	2/16	0.13 [0.03, 0.36]
	Belgrade, 1989[110]	4/22	0.18 [0.07, 0.39]
	Cicek, 2004 (Pethidine)[113]	22/84	0.26 [0.18, 0.36]
	Subtotal N=5	53/221	0.23 [0.17, 0.28]
Meperidine plus Antihistiamine	Duarte, 1992[94]	7/25	0.28 [0.14, 0.48]
	Stiell, 1991[66]	24/37	0.65 [0.49, 0.78]
	Lane, 1989[67]	4/22	0.18 [0.07, 0.39]
	Subtotal N=3	35/84	0.37 [0.08, 0.66]
Methotrimeprazine	Stiell, 1991[66]	31/37	0.84 [0.69, 0.92]
	Subtotal N=1	31/37	0.84 [0.69, 0.92]
Metoclopramide	Friedman, 2008[22]	5/38	0.13 [0.06, 0.27]
	Cicek, 2004[113]	17/85	0.20 [0.13, 0.30]
	Jones, 1996[91]	5/29	0.17 [0.08, 0.35]
	Cameron, 1995[65]	7/44	0.16 [0.08, 0.29]
	Subtotal N=4	34/196	0.17 [0.12, 0.22]
Metoclopramide plus Pethidine	Cicek, 2004[113]	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[86]	1/21	0.05 [0.01, 0.23]
	Subtotal N=1	1/21	0.05 [0.01, 0.23]
Nalbuphine	Tek, 1987[98]	14/23	0.61 [0.41, 0.78]
	Subtotal N=1	14/23	0.61 [0.41, 0.78]
Nalbuphine plus Hydroxyzine	Tek, 1987[98]	14/24	0.58 [0.39, 0.76]
	Subtotal N=1	14/24	0.58 [0.39, 0.76]
Prochlorperazine	Callan, 2008[75]	14/35	0.40 [0.26, 0.56]
	Friedman, 2008[22]	6/39	0.15 [0.07, 0.30]
	Miner, 2001[87]	1/86	0.01 [0.00, 0.06]
	Jones, 1996[91]	5/28	0.18 [0.08, 0.36]
	Jones, 1989[68]	7/42	0.17 [0.08, 0.31]
	Subtotal N=5	33/230	0.17 [0.04, 0.30]
Promethazine	Callan, 2008[75]	25/35	0.66 [0.49, 0.79]
	Subtotal N=1	25/35	0.66 [0.49, 0.79]
Sumatriptan	Friedman, 2006[79]	2/20	0.10 [0.03, 0.30]
	Wendt, 2006[57]	11/384	0.03 [0.02, 0.05]
	Cady, 1991[60]	15/547	0.03 [0.02, 0.04]
	Subtotal N=3	28/951	0.03 [0.02, 0.04]
Trimethobenzamide plus DHE	Friedman, 2006[79]	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 sulfate; N = number

Dizziness

Twenty-three studies reported dizziness as an adverse effect. Included in this category is postural hypertension, syncope, relative hypotension, orthostatic hypotension, fainting, head rushes and dizzy spells (Figure 35, Table 36).[19,20,22,43,53,57,58,60,65-68,72,76,86,97,98,100,106,109,110,113] The risk of becoming dizzy in those who received placebo was 5 percent (95% CI: 2 to 8 percent). The risk in those who received an active agent ranged from 2 percent (95% CI: 1 to 8 percent) to 80 percent (95% CI: 63 to 91 percent).

Figure 35. Risk of dizziness reported in acute migraine trials

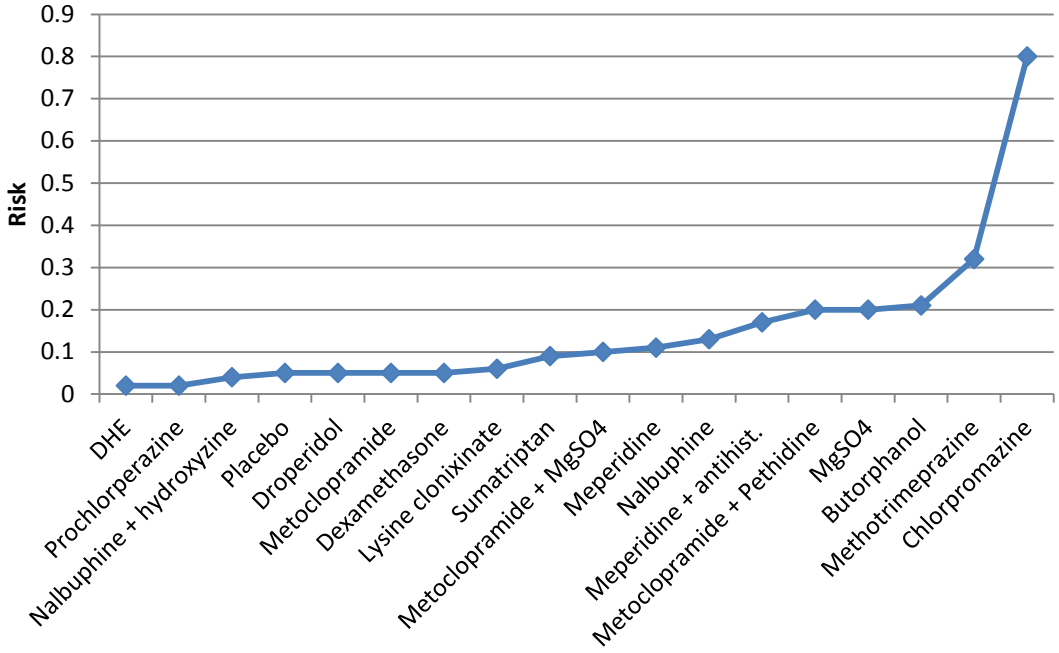


Table 36. Dizziness reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Cicek, 2004[113]	1/83	0.01 [0.00, 0.07]
	McEwen, 1987[97]	3/17	0.18 [0.06, 0.41]
	Krymchantowski, 2003[100]	1/12	0.08 [0.01, 0.35]
	Wendt, 2006[57]	10/193	0.05 [0.03, 0.09]
	Bigal, 2002[43]	10/30	0.33 [0.19, 0.51]
	Mushet, 1996[58]	2/79	0.03 [0.01, 0.09]
	Cady, 1991[60]	15/370	0.04 [0.02, 0.07]
	Silberstein, 2003[63]	3/61	0.05 [0.02, 0.14]
	Subtotal N=8	36/845	0.05 [0.02, 0.08]
Butorphanol	Belgrade, 1989[110]	4/19	0.21 [0.09, 0.43]
	Subtotal N=1	4/19	0.21 [0.09, 0.43]
Chlorpromazine	Bigal, 2002[43]	24/30	0.80 [0.63, 0.91]
	Subtotal N=1	24/30	0.80 [0.63, 0.91]
Standard abortive therapy plus dexamethasone	Donaldson, 2008[76]	9/57	0.16 [0.09, 0.43]
	Friedman, 2007[20]	3/106	0.03 [0.01, 0.08]
	Innes, 1999[19]	2/49	0.04 [0.01, 0.14]
	Jones, 2003[109]	1/34	0.03 [0.01, 0.15]
	Subtotal N=4	15/246	0.05 [0.01, 0.10]
DHE	Carleton, 1998[53]	2/85	0.02 [0.01, 0.08]
	Subtotal N=1	2/85	0.02 [0.01, 0.08]
Droperidol	Silberstein, 2003[63]	3/61	0.05 [0.02, 0.14]
	Subtotal N=1	3/61	0.05 [0.02, 0.14]
Lysine clonixinate	Krymchantowski, 2003[100]	1/17	0.06 [0.01, 0.27]
	Subtotal N=1	1/17	0.06 [0.01, 0.27]
Meperidine	Carleton, 1998[53]	13/85	0.15 [0.09, 0.24]
	Belgrade, 1989[110]	1/22	0.05 [0.01, 0.22]
	Subtotal N=2	14/107	0.11 [0.00, 0.21]

Table 36. Dizziness reported in acute migraine trials (continued)

Intervention	Author, Year	n/N	Risk (95% CI)
Meperidine plus Antihistamine	Stiell, 1991[66]	11/37	0.30 [0.17, 0.46]
	Lane, 1989[67]	1/22	0.05 [0.01, 0.22]
	Subtotal N=2	12/59	0.17 [0.00, 0.41]
Methotrimeprazine	Stiell, 1991[66]	12/37	0.32 [0.20, 0.49]
	Subtotal N=1	12/37	0.32 [0.20, 0.49]
Metoclopramide	Friedman, 2008[22]	2/38	0.05 [0.01, 0.17]
	Cicek, 2004[113]	3/85	0.04 [0.01, 0.10]
	Corbo, 2001[86]	1/23	0.04 [0.01, 0.21]
	Cameron, 1995[65]	4/44	0.09 [0.04, 0.21]
	Subtotal N=4	10/190	0.05 [0.01, 0.08]
Metoclopramide plus pethidine	Cicek, 2004[113]	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[86]	2/21	0.10 [0.03, 0.29]
	Subtotal N=1	2/21	0.10 [0.03, 0.29]
$MgSO_4$	Demirkaya, 2001[72]	3/15	0.20 [0.07, 0.45]
	Subtotal N=1	3/15	0.20 [0.07, 0.45]
Nalbuphine	Tek, 1987[98]	3/23	0.13 [0.05, 0.32]
	Subtotal N=1	3/23	0.13 [0.05, 0.32]
Nalbuphine plus hydroxyzine	Tek, 1987[98]	1/24	0.04 [0.01, 0.20]
	Subtotal N=1	1/24	0.04 [0.01, 0.20]
Prochlorperazine	Jones, 1989[68]	1/42	0.02 [0.00, 0.12]
	Subtotal N=1	1/42	0.02 [0.00, 0.12]
Sumatriptan	Wendt, 2006[57]	40/384	0.10 [0.08, 0.14]
	Mushet, 1996[58]	3/79	0.04 [0.01, 0.11]
	Akpunonu, 1995[106]	8/88	0.09 [0.05, 0.17]
	Cady, 1991[60]	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 sulfate; N = number

Local Reaction

There were 14 studies that measured local reactions including pain or swelling at the injection site and IV site irritation (Figure 36, Table 37).[21,53,57,58,60,61,67,76,86,89,98,100,109] 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 36. Risk of local reaction reported in acute migraine trials

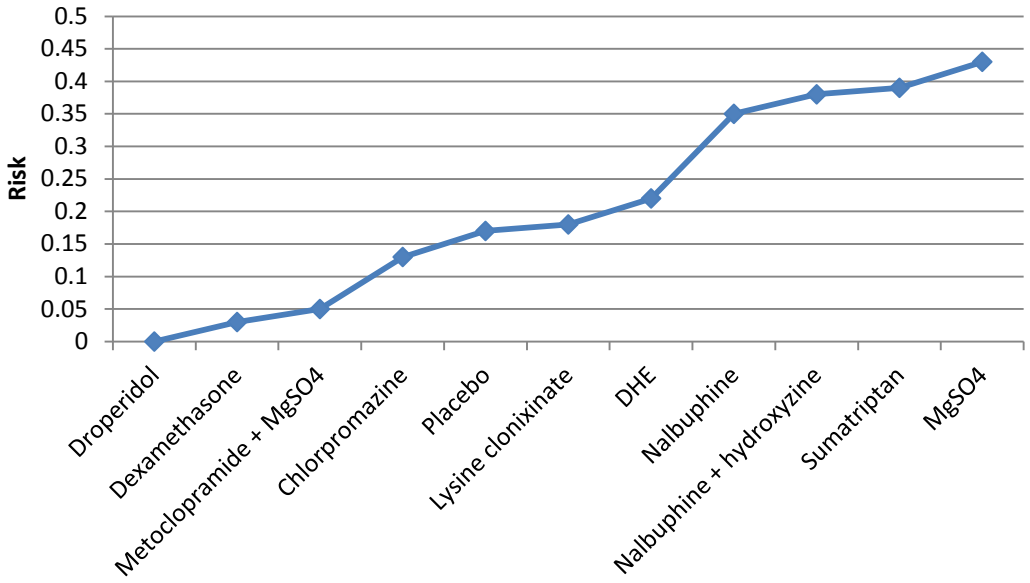


Table 37. Local reaction reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Tek, 1987[98]	4/24	0.17 [0.07, 0.36]
	Wendt, 2006[57]	28/193	0.15 [0.10, 0.20]
	Mushet, 1996[58]	14/79	0.18 [0.11, 0.28]
	Cady, 1991[60]	88/370	0.24 [0.20, 0.28]
	Silberstein, 2003[63]	6/61	0.10 [0.05, 0.20]
	Subtotal N=5	140/727	0.17 [0.11, 0.22]
Chlorpromazine	Lane, 1989[67]	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[21]	2/64	0.03 [0.01, 0.11]
	Donaldson, 2008[76]	2/57	0.04 [0.01, 0.12]
	Jones, 2003[109]	1/34	0.03 [0.01, 0.15]
	Subtotal N=3	5/155	0.03 [0.00, 0.06]
DHE	Carleton, 1998[53]	6/85	0.07 [0.03, 0.15]
	Winner, 1996[61]	57/152	0.38 [0.30, 0.45]
	Subtotal N=2	63/237	0.22 [0.00, 0.52]
Droperidol	Silberstein, 2003[63]	0/61	0.00 [0.00, 0.04]
	Subtotal N=1	0/61	0.00 [0.00, 0.04]
Lysine clonixinate	Krymchantowski, 2003[100]	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[86]	1/21	0.05 [0.01, 0.23]
	Subtotal N=1	1/21	0.05 [0.01, 0.23]
$MgSO_4$	Ginder, 2000[89]	3/7	0.43 [0.16, 0.75]
	Subtotal N=1	3/7	0.43 [0.16, 0.75]
Nalbuphine	Tek, 1987[98]	8/23	0.35 [0.19, 0.55]
	Subtotal N=1	8/23	0.35 [0.19, 0.55]
Nalbuphine plus Hydroxyzine	Tek, 1987[98]	9/24	0.38 [0.21, 0.57]
	Subtotal N=1	9/24	0.38 [0.21, 0.57]
Sumatriptan	Wendt, 2006[57]	165/384	0.43 [0.38, 0.48]
	Mushet, 1996[58]	27/79	0.34 [0.25, 0.45]
	Cady, 1991[60]	321/547	0.59 [0.55, 0.63]
	Winner, 1996[61]	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 sulfate; N = number

Skin Reactions

Ten studies measured skin reactions to the interventions administered (Figure 37, Table 38).[32,57,58,60,72,83,86,110,113] Included in this category was 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 37. Risk of skin reaction reported in acute migraine trials

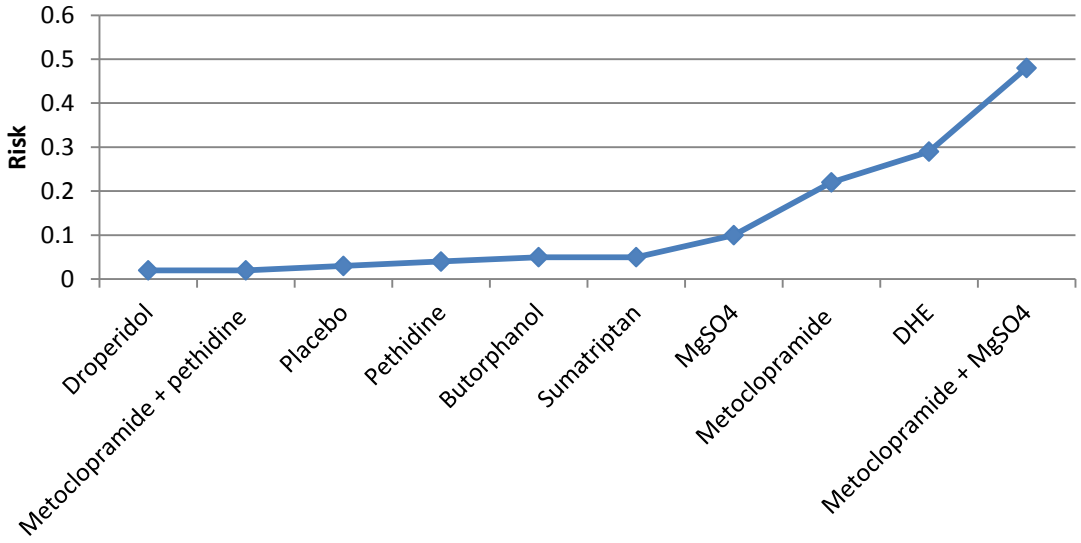


Table 38. Skin reaction reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Wendt, 2006[57]	7/193	0.04 [0.02, 0.07]
	Mushet, 1996[58]	2/79	0.03 [0.01, 0.09]
	Silberstein, 2003[63]	3/61	0.05 [0.02, 0.14]
	Subtotal N=3	12/333	0.03 [0.01, 0.06]
Butorphanol	Belgrade, 1989[110]	1/19	0.05 [0.01, 0.25]
	Subtotal N=1	1/19	0.05 [0.01, 0.25]
DHE	Belgrade, 1989[110]	6/21	0.29 [0.14, 0.50]
	Subtotal N=1	6/21	0.29 [0.14, 0.50]
Droperidol	Silberstein, 2003[63]	1/61	0.02 [0.003, 0.09]
	Subtotal N=1	1/61	0.02 [0.003, 0.09]
Metoclopramide	Corbo, 2001[86]	5/23	0.22 [0.10, 0.42]
	Subtotal N=1	5/23	0.22 [0.10, 0.42]
Metoclopramide plus Pethidine	Cicek, 2004[113]	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[86]	10/21	0.48 [0.28, 0.68]
	Subtotal N=1	10/21	0.48 [0.28, 0.68]
$MgSO_4$	Demirkaya, 2001[72]	2/15	0.13 [0.04, 0.38]
	Cete, 2004[83]	3/36	0.08 [0.03, 0.22]
	Subtotal N=2	5/51	0.10 [0.01, 0.18]
Pethidine	Cicek, 2004[113]	3/84	0.04 [0.01, 0.10]
	Subtotal N=1	3/84	0.04 [0.01, 0.10]
Sumatriptan	Kelly, 1997[32]	1/20	0.05 [0.01, 0.24]
	Wendt, 2006[57]	10/384	0.03 [0.01, 0.05]
	Mushet, 1996[58]	4/79	0.05 [0.02, 0.12]
	Cady, 1991[60]	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 sulfate; N = number

Extrapyramidal Symptoms

Six studies reported extrapyramidal symptoms as a result of treatment.[58,66,79,82,83,87] Included in this category are dystonic reactions, stiff neck, abnormal movements, and muscle twitching. The symptoms varied across studies and included muscle cramps,[58] dystonia,[66,87] muscle twitching,[66] stiffness or abnormal movements,[82] and stiff neck.[79] 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

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Mushet, 1996[58]	1/79	0.01 [0.00, 0.07]
	Silberstein, 2003[63]	1/61	0.02 [0.003, 0.09]
	Subtotal N=2	2/140	0.01 [0.00, 0.04]
Droperidol	Miner, 2001[87]	1/82	0.01 [0.00, 0.07]
	Silberstein, 2003[63]	1/61	0.02 [0.003, 0.09]
	Subtotal N=2	2/143	0.01 [0.00, 0.04]
Methotrimeprazine	Stiell, 1991[66]	3/37	0.08 [0.03, 0.21]
	Subtotal N=1	3/37	0.08 [0.03, 0.21]
Metoclopramide	Friedman, 2005[82]	3/40	0.08 [0.03, 0.20]
	Cete, 2004[83]	1/37	0.03 [0.00, 0.14]
	Subtotal N=2	4/77	0.04 [0.00, 0.10]
Sumatriptan	Friedman, 2006[79]	3/20	0.15 [0.05, 0.36]
	Friedman, 2005[82]	7/38	0.18 [0.09, 0.33]
	Mushet, 1996[58]	2/79	0.03 [0.01, 0.09]
	Subtotal N=3	12/137	0.11 [0.00, 0.22]

CI = confidence interval; N = number

Chest Symptoms

Five studies assessed chest symptoms, which included palpitations, arrhythmia, and irregular heartbeat.[32,57,58,61,106] See Table 40 for a summary of results.

Table 40. Chest symptoms reported in migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Wendt, 2006[57]	2/193	0.01 [0.00, 0.04]
	Subtotal N=1	2/193	0.01 [0.00, 0.04]
Chlorpromazine	Kelly, 1997[32]	1/23	0.04 [0.01, 0.21]
	Subtotal N=1	1/23	0.04 [0.01, 0.21]
DHE	Winner, 1996[61]	14/152	0.09 [0.06, 0.15]
	Subtotal N=1	14/152	0.09 [0.06, 0.15]
Sumatriptan	Wendt, 2006[57]	20/384	0.05 [0.03, 0.08]
	Mushet, 1996[58]	5/79	0.06 [0.03, 0.14]
	Akpunonu, 1995[106]	5/88	0.06 [0.02, 0.13]
	Winner, 1996[61]	9/158	0.06 [0.03, 0.10]
	Subtotal N=4	39/709	0.05 [0.04, 0.07]

CI = confidence interval; DHE = dihydroergotamine; N = number

Anxiety

Five studies reported anxiety and related adverse effects, including mood change, moodiness, agitation, and insomnia.[57,60,75,76,78] See Table 41 for a summary of results.

Table 41. Anxiety reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Cady, 1991[60]	16/370	0.04 [0.03, 0.07]
	Silberstein, 2003[63]	2/61	0.03 [0.01, 0.11]
	Subtotal N=2	18/431	0.04 [0.02, 0.06]
Standard abortive therapy plus Dexamethasone	Donaldson, 2008[76]	3/57	0.05 [0.02, 0.14]
	Baden, 2006[78]	1/31	0.03 [0.01, 0.16]
	Subtotal N=2	4/88	0.04 [0.00, 0.09]
Droperidol	Silberstein, 2003[63]	10/61	0.16 [0.09, 0.28]
	Subtotal N=1	10/61	0.16 [0.09, 0.28]
Prochlorperazine	Callan, 2008[75]	13/35	0.37 [0.23, 0.54]
	Subtotal N=1	13/35	0.37 [0.23, 0.54]
Promethazine	Callan, 2008[75]	8/35	0.23 [0.12, 0.39]
	Subtotal N=1	8/35	0.23 [0.12, 0.39]
Sumatriptan	Wendt, 2006[57]	4/384	0.01 [0.00, 0.03]
	Cady, 1991[60]	6/547	0.01 [0.01, 0.02]
	Subtotal N=2	10/931	0.01 [0.00, 0.02]

CI = confidence interval; N = number

Digestion Issues

Two studies assessed digestion issues that were attributed to the interventions.[20,53] Included in this category were any reports on dyspepsia, heartburn, epigastric discomfort, and diarrhea. See Table 42 for a summary of results.

Table 42. Digestion issues reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Friedman, 2007[20]	3/99	0.03 [0.01, 0.09]
	Subtotal N=1	3/99	0.03 [0.01, 0.09]
DHE	Carleton, 1998[53]	10/85	0.12 [0.07, 0.20]
	Subtotal N=1	10/85	0.12 [0.07, 0.20]
Meperidine	Carleton, 1998[53]	4/85	0.05 [0.02, 0.11]
	Subtotal N=1	4/85	0.05 [0.02, 0.11]

CI = confidence interval; DHE = dihydroergotamine; N = number

Emergence Reactions

Two studies reported emergence reactions that resulted from the administration of the interventions.[32,58] Included in this category were unpleasant dreams and nightmares. See Table 43 for a summary of the results.

Table 43. Emergence reactions reported in acute migraine trials

Intervention	Author, Year	n/N	Risk (95% CI)
Placebo	Mushet, 1996[58]	2/79	0.03 [0.01, 0.09]
	Subtotal N=1	2/79	0.03 [0.01, 0.09]
Sumatriptan	Kelly, 1997[32]	1/20	0.05 [0.01, 0.24]
	Mushet, 1996[58]	1/79	0.01 [0.00, 0.07]
	Subtotal N=2	2/99	0.02 [0.00, 0.05]

CI = confidence interval; N = number

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.

This section addresses the development akathisia following the administration of phenothiazines plus anticholinergic agents compared with metoclopramide plus anticholinergic agents. Different drugs are used to combat akathisia. While most are anticholinergics, some have antihistamine *and* anticholinergic properties. These agents have been classified as anticholinergics in this report.

One study[22] examined the differences in the development of akathisia when metoclopramide or phenothiazines were used with anticholinergic agents (Table 6). In this study, participants were administered either prochlorperazine or metoclopramide, both accompanied by 25 mg of IV diphenhydramine.[227670] 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).

In another study, participants were administered prochlorperazine plus diphenhydramine or prochlorperazine alone (Table 9).[29] There was no statistically significant difference between groups in the development of akathisia symptoms (OR = 0.46; 95% CI: 0.17, 1.28) (Table 44).

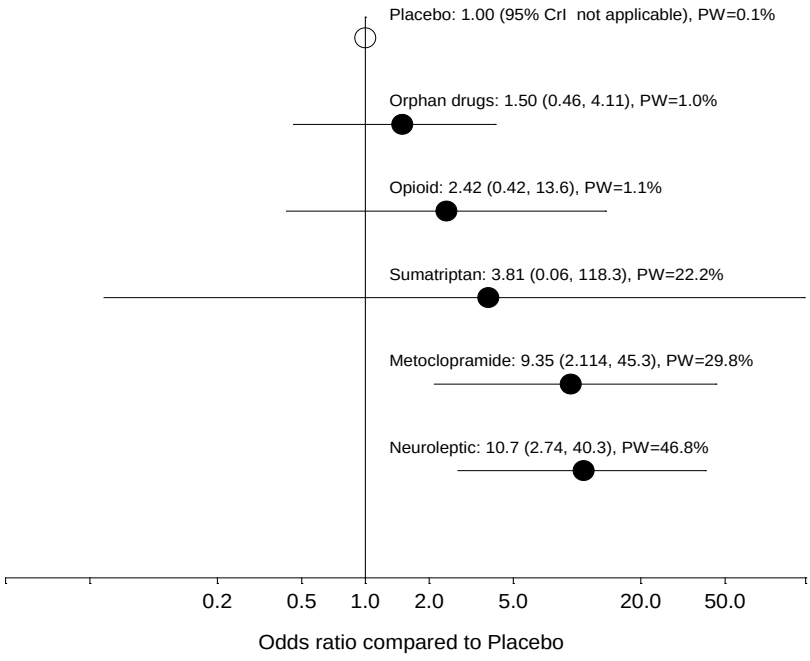
Table 44. Strength of evidence for the development of akathisia when anticholinergic agents are added to metoclopramide or phenothiazines

Comparison	Outcome (N Studies; N Patients)	Strength of Evidence Domains				Strength of Evidence
		ROB	Consistency	Direct	Precision	
Metoclopramide + DPH vs. prochlor-perazine + DPH	Akathisia (1; 77)	Moder ate	Unknown	Direct	Imprecise	Insufficient
Prochlorperazine + DPH vs. prochlorperazine	Akathisia (1; 58)	Low	Unknown	Direct	Imprecise	Insufficient

DPH = diphenhydramine; N = number; ROB = risk of bias

We conducted a post hoc mixed treatment analysis of 15 studies that reported akathisia as an adverse event. In addition to neuroleptics and metoclopramide, other interventions included opioids, sumatriptan, and orphan agents (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 38). See Appendix F for the network diagram.

Figure 38. Mixed treatment analysis of studies that reported akathisia as an adverse effect



PB = probability

Key Question 5: Effectiveness and Safety of Parenteral Pharmacological Interventions in Different Subgroups

No studies presented results for the subgroups sex, race and duration of headaches. There were some data reported for the subgroup of patients who did not respond to treatment.

The detailed summary 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 studies (43 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 their patients after discharge, so it is difficult to determine the relationship between non-response and relapse outcomes. Several studies found that patients who achieved complete relief in the ED were less likely to have recurrence of headache within 48 hours.[68,117] 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.[21]After multivariate adjustment, other investigators identified the following independent predictors of poor 24-hour outcomes: severe baseline pain, baseline nausea, screening positive for depression, and longer duration of headache.[118]

Key Question 6: Subpopulations in Studies Assessing the Effectiveness of Corticosteroids in Prevention of Migraine Relapse

One study reported no difference in response between men and women in the prevention of relapse at 24-48 hours after ED discharge.[21] No studies presented results for by race or ethnicity.

Several studies conducted an a priori subgroup analysis based on duration of headache. In the first,[20] the authors compared patients who had an acute migraine lasting longer than 72 hours (n = 45) and 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 who received 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.[21] 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, a third study demonstrated an association between increased headache duration and severe recurrent headache, suggesting that the risk ratio of recurrent severe headache increases by about one percent per hour of headache duration.[19] 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 ≤2).[21] 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 compared with those whose pain was assessed with a VAS ≤2 at discharge (adjusted OR=2.4; 95% CI: 1.1, 5.4).

Summary and Discussion

Key Findings and Strength of Evidence

This comparative effectiveness review (CER) 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 emergency department (ED) or an equivalent setting. The strength of the body of evidence for key effectiveness outcomes is summarized by intervention below.

For the majority of studies pain relief or severity was the primary outcome. There were nine different classes of drugs investigated in 71 studies. The interventions included metoclopramide, neuroleptics, ergotamines, nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, corticosteroids, triptans, magnesium sulfate ($MgSO_4$), and antihistamines. There were several studies that examined combinations of active agents compared with other active agents. The mixed treatment analysis included a group of drugs collectively referred to as "orphan agents".

Data were provided primarily from randomized controlled trials (RCTs). Risk of bias assessment showed that 28 percent of the trials had low risk of bias and 61 percent had unclear risk of bias. Sample sizes varied but they were generally small, 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 (VAS), there was a clear indication that combinations of anti-migraine medications and monotherapy with neuroleptic agents out-performed other active agents. The pain relief data must be weighed carefully with the data on adverse 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 mixed treatment analysis showed that the most effective treatments were combination therapy (i.e., dihydroergotamine [DHE] added to either neuroleptics or metoclopramide) or neuroleptic monotherapy (low SOE) with a pain reduction of approximately 40 mm on the VAS. Metoclopramide monotherapy, opioids, and NSAIDs were the next most effective treatments with a pain reduction of approximately 24 mm (low SOE). Other agents (e.g., DHE, triptans, orphan agents) were less effective with a pain reduction of approximately 12-16 mm (low SOE).

Metoclopramide was compared with placebo in six trials and with other active treatments in nine trials (Table 45). Metoclopramide was significantly more effective than placebo for pain relief (moderate strength of evidence). Metoclopramide was generally less effective than neuroleptics for pain relief (low strength of evidence). Results for pain relief were inconsistent when comparing metoclopramide monotherapy with other active treatments (excluding neuroleptics). Single trials compared metoclopramide with $MgSO_4$, ondansetron plus paracetemol, pethidine, and sumatriptan (insufficient 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.

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

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain intensity–VAS	Metoclopramide vs. placebo (5 RCTs)	Moderate	Significant effect in favor of metoclopramide (MD = -21.88; 95% CI: -27.38, -16.38; I^2 = 0%)
Headache relief	Metoclopramide vs. placebo (1 RCT)	Insufficient	Significant effect in favor of metoclopramide (RR = 3.34; 95% CI: 1.50, 8.01)
Headache recurrence	Metoclopramide vs. placebo (1 RCT)	Insufficient	No significant difference between groups (RR = 0.82; 95% CI: 0.51, 1.32)
Pain improvement	Metoclopramide + DHE or dexamethasone vs. placebo (1 RCT, 3 arms)	Insufficient	Significant effect in favor of metoclopramide + other; Results not pooled
Change in pain–VAS	Metoclopramide vs. neuroleptics (4 RCTs)	Low	Significant effect in favor of neuroleptics (MD = 16.45; 95%CI: 2.08, 30.83; I^2 = 81%)
Change in pain–VAS	Metoclopramide vs. prochlorperazine (2 RCTs)	Low	No significant difference between groups (MD = 19.27; 95% CI: -8.85, 47.38; I^2 = 90%)
Headache recurrence	Metoclopramide vs. prochlorperazine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.41; 95% CI: 0.11, 1.51)
Change in pain–VAS	Metoclopramide + DPH vs. prochlorperazine + DPH (1 RCT)	Insufficient	No significant difference between groups (MD = 3.0; 95% CI: -9.75, 15.75)
Change in pain–VAS	Metoclopramide vs. chlorpromazine (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = 25.0; 95% CI: 12.14, 37.86)
Sustained headache relief	Prochlorperazine + DPH vs. metoclopramide + DPH (1 RCT)	Insufficient	No significant difference between groups (RR = 0.73; 95% CI: 0.48, 1.12)
Pain free (2 hrs)	Prochlorperazine + DPH vs. metoclopramide + DPH (1 RCT)	Insufficient	No significant difference between groups (RR = 0.71; 95% CI: 0.44, 1.16)
Headache relief (2 hrs)	Prochlorperazine + DPH vs. metoclopramide + DPH (1 RCT)	Insufficient	No significant difference between groups (RR = 0.91; 95% CI: 0.73, 1.12)
Change in pain (<2 hrs)–VAS	Metoclopramide vs. $MgSO_4$ (1 RCT)	Insufficient	No significant difference between groups (MD = -5.0; 95% CI: -15.80, 5.80)
Headache recurrence	Metoclopramide vs. $MgSO_4$ (1 RCT)	Insufficient	No significant difference between groups (MD = 0.82; 95% CI: 0.51, 1.33)
Change in pain (<2 hrs)–VAS	Metoclopramide vs. pethidine (1 RCT)	Insufficient	Significant effect in favor of metoclopramide (MD = -10.0; 95% CI: -19.21, -0.79)
Change in pain (<2 hrs)–VAS	Metoclopramide vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = -9.0; 95% CI: -20.99, 2.99)
Change in pain intensity (24 hrs)–NRS	Metoclopramide vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 1.10; 95% CI: -0.60, 2.80)
Change in pain (<2 hrs)–-VAS	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 17.0; 95% CI: -0.08, 34.08)
Pain free response (1 hr)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.43; 95% CI: 0.13, 1.43)

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

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain free response (2 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.67; 95% CI: 0.29, 1.52)
Pain free response (24 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.78; 95% CI: 0.36, 1.68)
Headache response (1 hr)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.88; 95% CI: 0.61, 1.26)
Headache response (2 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.94; 95% CI: 0.71, 1.25)
Headache response (24 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 1.13; 95% CI: 0.83, 1.55)
Change in pain intensity (24 hrs)–-NRS	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 0.40; 95% CI: -1.50, 2.30)

CI = confidence interval DPH = diphenhydramine; MD = mean difference; $MgSO_4$ = magnesium sulfate; NRS = numeric rating scale; RCT = randomized controlled trial; RR = risk ratio

Neuroleptics were compared with placebo in seven trials and with other active treatments in 17 trials (Table 46). 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 pain relief, but this wasn't consistent across studies. More patients who received droperidol experienced headache relief compared with patients who received prochlorperazine based on two RCTs (moderate strength of evidence). For all other head to head comparisons, single trials compared different neuroleptics with anticonvulsants, corticosteroids, dihydroergotamine (DHE), other neuroleptics, NSAIDs, opioids, somatostatin analog, sumatriptan, and lidocaine (insufficient strength of evidence). Single trials compared a neuroleptic agent with another active agent for headache recurrence (insufficient strength of evidence). The mixed treatment analysis demonstrated that monotherapy with neuroleptic agents was one of the more effective treatment options (low strength of evidence).

Table 46. Summary of the strength of evidence for the effectiveness of neuroleptics versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
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%)
Headache relief (1 hr)	Neuroleptic vs. placebo (5 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 2.69, 95% CI: 1.66, 4.34; I^2 = 76%)
Pain free (1 hr)	Neuroleptic vs. placebo (4 RCTs)	Moderate	Significant effect in favor of neuroleptics (RR = 3.38; 95% CI: 1.16, 9.83; I2 = 90%).
Headache recurrence (24 hrs)	Neuroleptic vs. placebo (2 RCTs)	Low	No significant difference between groups (RR = 0.46; 95% CI: 0.19, 1.10; I^2 = 78%)
Patient satisfaction	Neuroleptics vs. placebo (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (RR = 3.28; 95% CI: 1.10, 9.82)
Change in pain–VAS	Metoclopramide vs. neuroleptics (4 RCTs)	Low	Significant effect in favor of neuroleptics (MD = 16.45; 95%CI: 2.08, 30.83; I^2 = 81%)
Change in pain–VAS	Metoclopramide vs. prochlorperazine (2 RCTs)	Low	No significant difference between groups (MD = 19.27; 95% CI: -8.85, 47.38; I^2 = 90%)
Headache recurrence	Metoclopramide vs. prochlorperazine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.41; 95% CI: 0.11, 1.51)
Change in pain–VAS	Prochlorperazine vs. sodium valproate (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -55.5; 95% CI: -81.14, -29.86)
Change in pain–VAS	Prochlorperazine vs. $MgSO_4$ (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -23.0; 95% CI: -44.67, -1.33)
Change in pain-VAS	Metoclopramide vs. chlorpromazine (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = 25.0; 95% CI: 12.14, 37.86)
Change in pain–VAS	Chlorpromazine vs. DHE (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = -40.0; -47.12, -32.88)
Headache relief	Chlorpromazine vs. DHE (1 RCT)	Insufficient	No significant difference between groups (RR = 1.44; 95% CI: 0.59, 3.56)
Change in pain–VAS	Chlorpromazine vs. lidocaine (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = -27.5; 95% CI: -33.85, -21.15)
Headache relief	Chlorpromazine vs. lidocaine (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (RR = 4.33; 95% CI: 1.02, 18.41)
Change in pain–VAS	Prochlorperazine vs. ketorolac (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -19.0; 95% CI: -34.97, -3.03)
Change in pain–VAS	Chlorpromazine hydrochloride vs. ketorolac tropethamine (1 RCT)	Insufficient	No significant difference between groups (MD = -5.30; 95% CI: -24.89, 14.29)
Change in pain–VAS	Droperidol vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (MD = -10.0; 95% CI: -30.03, 10.03)
Change in pain–VAS	Methotrimeprazine vs. meperidine + dimenhydrinate (1 RCT)	Insufficient	No significant difference between groups (MD = 6.30; 95% CI: -4.77, 17.37)
Pain intensity–VAS	Meperidine + dimenhydrinate vs methotrimeprazine (1 RCT)	Insufficient	No significant difference between groups (MD = 15.0; 95% CI: -2.75, 32.75)
Change in pain–VAS	Chlorpromazine vs. meperidine + dimenhydrinate (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = -26.1; 95% CI: -40.1, -12.1)
Change in pain–VAS	Prochlorperazine + DPH vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -23.0; 95% CI: -35.5, -10.5)

Table 46. Summary of the strength of evidence for the effectiveness of neuroleptics versus placebo or an active treatment (Key Question 1) (continued)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Change in pain–VAS	Metoclopramide + DPH vs. prochlorperazine + DPH (1 RCT)	Insufficient	No significant difference between groups (MD = 3.0; 95% CI: -9.75, 15.75)
Sustained headache relief	Prochlorperazine + DPH vs. Metoclopramide + diphnehydramine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.73; 95% CI: 0.48, 1.12)
Pain free (2 hrs)	Prochlorperazine + DPH vs. Metoclopramide + DPH (1 RCT)	Insufficient	No significant difference between groups (RR = 0.71; 95% CI: 0.44, 1.16)
Headache relief (2 hrs)	Prochlorperazine + DPH vs. Metoclopramide + DPH (1 RCT)	Insufficient	No significant difference between groups (RR = 0.91; 95% CI: 0.73, 1.12)
Change in pain–VAS	Prochlorperazine vs. promethazine (1 RCT)	Insufficient	No significant difference between groups (MD = -19.05; 95% CI: -67.31, 29.21)
Headache recurrence	Prochlorperazine vs. promethazine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.71; 95% CI: 0.45, 1.14)
Change in pain–VAS	Prochlorperazine vs. droperidol (2 RCTs)	Low	No significant difference between groups (MD = 9.12; 95% CI: -8.62, 26.86)
Headache relief	Prochlorperazine vs. droperidol (2 RCTs)	Moderate	Significant effect in favor of droperidol (RR = 0.81; 95% CI: 0.68, 0.98)
Pain free at 30 mins (1; 95)	Prochlorperazine vs. droperidol (1 RCT)	Insufficient	No significant difference between groups (RR = 0.71; 95% CI: 0.45, 1.11)
Change in pain–VAS	Prochlorperazine vs. octreotide (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -17.2; 95% CI: -32.13, -2.27)
Headache relief	Prochlorperazine vs. octreotide (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (RR = 1.59; 95% CI: 1.08, 2.34)
Change in pain–VAS	Olanzapine vs. droperidol (1 RCT)	Insufficient	No significant difference between groups (MD = -6.2; 95% CI: -17.16, 4.76)
Pain free (30 min)	Haloperidol vs. dexamethasone (1 RCT)	Insufficient	No significant difference between groups (RR = 2.68; 95% CI: 0.62, 11.64)
Headache recurrence	Haloperidol vs. dexamethasone (1 RCT)	Insufficient	No significant difference between groups (no events in either group)

CI = confidence interval; DHE = dihydroergotamine; DPH = diphenhydramine; MD = mean difference; $MgSO_4$ = magnesium sulfate; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

NSAIDs were compared with placebo in two trials and with other active treatments in nine trials (Table 47). NSAIDs were more effective than placebo for pain relief (moderate strength of evidence). There was insufficient strength of evidence for headache recurrence when NSAIDs were compared with placebo. Results were mixed for NSAIDs compared with other active agents for pain relief. Single trials compared NSAIDs with meperidine, sumatriptan, paracetamol, DHE, and tramadol (insufficient strength of evidence). 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.

Table 47. Summary of the strength of evidence for the effectiveness of NSAIDs versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain free at 1-2 hrs	NSAIDs vs. placebo (2 RCTs)	Moderate	Significant effect in favor of NSAIDs (RR = 2.74; 95% CI: 1.26, 5.98; I2 = 47%)
Change in pain-VAS	Ketorolac vs. meperidine + promethazine (1 RCT)	Insufficient	No significant difference between groups (MD = 0.00; 95% CI: -7.51, 7.51)
Pain response	Ketorolac vs. meperidine + promethazine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.81; 95% CI: 0.49, 1.31)
Change in pain-VAS	Ketorolac vs. meperidine + hydroxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = 5.20; 95% CI: -10.08, 20.48)
Pain response	Ketorolac vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.53; 95% CI: 0.24, 1.20)
Pain free (1-2 hrs)	Ketorolac vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.21; 95% CI: 0.03, 1.62)
Pain intensity-VAS	Ketorolac vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of ketorolac (MD = -48.53; 95% CI: -65.54, -31.51)
Change in pain-VAS	Prochlorperazine vs. ketorolac (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -19.0; 95% CI: -34.97, -3.03)
Change in pain-VAS	Chlorpromazine hydrochloride vs. ketorolac tropethamine (1 RCT)	Insufficient	No significant difference between groups (MD = -5.30; 95% CI: -24.89, 14.29)
Pain response	Lysine acetylsalicylic acid vs. ergotamine (1 RCT)	Insufficient	Significant effect in favor of lysine acetylsalicylic acid (RR = 1.92; 95 % CI: 1.10, 3.36)
Pain intensity-VAS	DHE vs. diclofenac (1 RCT)	Insufficient	No significant difference between groups (MD = -13.00; 95% CI: -28.52, 2.52)
Pain response	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.0; 95% CI: 0.73, 1.36)
Pain free (1-2 hrs)	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.29; 95% CI: 0.60, 2.77)
Headache recurrence	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.50; 95% CI: 0.28, 8.04)
Pain free (1-2 hrs)	Diclofenac sodium vs.paracetemol (1 RCT)	Insufficient	Significant effect in favor of diclofenac sodium (RR = 5.08; 95% CI: 2.57, 10.03)

CI = confidence interval; DHE = dihydroergotamine; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

Opioids were compared with placebo in three trials and with other active treatments in 13 trials (Table 48). 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. Single trials compared opioids with hydroxyzine, other opioids (i.e., nalbuphine, meperidine), methotrimeprazine, metoclopramide, methotrimeprazine, neuroleptic agents, NSAIDs, and DHE (insufficient strength of evidence). 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.

Table 48. Summary of the strength of evidence for the effectiveness of opioids versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain intensity–VAS	Opioids vs. placebo (3 RCTs)	Moderate	Significant effect in favor of opioids (MD = -16.73; 95% CI: -24.12, -9.33; I^2= 0%)
Pain intensity–VAS	Nalbuphine vs. nalbuphine + hydroxyzine (1RCT)	Insufficient	No significant difference between groups (MD = -15.80; 95% CI: -32.66, 1.06)
Pain intensity–VAS	Butorphanol vs meperidine + hydroxyzine (1 RCT)	Insufficient	Significant effect in favor of Butorphanol (MD = -17.00; 95% CI: -31.41, -2.59)
Pain intensity-VAS	DHE vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (MD = -2.20; 95% CI: -10.03, 14.43)
Pain response	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.0; 95% CI: 0.73, 1.36)
Pain free (1-2 hrs)	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.29; 95% CI: 0.60, 2.77)
Headache recurrence	Diclofenac vs. tramadol (1 RCT)	Insufficient	No significant difference between groups (RR = 1.50; 95% CI: 0.28, 8.04)
Change in pain-VAS	Ketorolac vs. meperidine + promethazine (1 RCT)	Insufficient	No significant difference between groups (MD = 0.00; 95% CI: -7.51, 7.51)
Pain response	Ketorolac vs. meperidine + promethazine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.81; 95% CI: 0.49, 1.31)
Change in pain-VAS	Ketorolac vs. meperidine + hydroxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = 5.20; 95% CI: -10.08, 20.48)
Pain response	Ketorolac vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.53; 95% CI: 0.24, 1.20)
Pain free (1-2 hrs)	Ketorolac vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (RR = 0.21; 95% CI: 0.03, 1.62)
Pain intensity–VAS	Nalbuphine vs hydoxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = -17.70; 95% CI: -36.85.14,1.45)
Pain intensity–VAS	Nalbuphine + hydroxyzine vs. Hydroxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = -1.90; 95% CI: -18.92, 15.12)
Pain intensity–VAS	Meperidine + dimenhydrinate vs methotrimeprazine (1 RCT)	Insufficient	No significant difference between groups (MD = 15.0; 95% CI: -2.75, 32.75)
Change in pain-VAS	Methotrimeprazine vs. meperidine + dimenhydrinate (1 RCT)	Insufficient	No significant difference between groups (MD = 6.30; 95% CI: -4.77, 17.37)
Pain intensity–VAS	Morphine vs dexamethasone (1 RCT)	Insufficient	Significant effect in favor of morphine (MD = -8.20; 95% CI: -12.58, -3.82)
Change in pain-VAS	Droperidol vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (MD = -10.0; 95% CI: -30.03, 10.03)
Change in pain-VAS	Chlorpromazine vs. meperidine + dimenhydrinate 1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = -26.1; 95% CI: -40.1, -12.1)

CI = confidence interval; DHE = dihydroergotamine; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

DHE was compared with other active treatments in five trials (Table 49). Results were mixed for pain relief. Single trials compared DHE with meperidine, neuroleptics agents, sumatriptan, lidocaine, and lysine acetylsalicylic acid (insufficient strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing DHE with other active agents. The mixed treatment analysis demonstrated that DHE monotherapy was similarly effective to orphan agents and anti-nauseants, but less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence).

Table 49. Summary of the strength of evidence for the effectiveness of DHE versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain intensity-VAS	DHE vs. meperidine (1 RCT)	Insufficient	No significant difference between groups (MD = -2.20; 95% CI: -10.03, 14.43)
Pain intensity-VAS	DHE vs. diclofenac (1 RCT)	Insufficient	No significant difference between groups (MD = -13.00; 95% CI: -28.52, 2.52)
Headache relief (1 hr)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (RR = 0.73; 95% CI: 0.61, 0.86)
Headache relief (2 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (RR = 0.86; 95% CI: 0.76, 0.96)
Headache relief (3 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.96; 95% CI: 0.88, 1.04)
Headache relief (4 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 1.03; 95% CI: 0.93, 1.13)
Headache relief (24 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of DHE (RR = 1.17; 95% CI: 1.05, 1.30)
Headache recurrence	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of DHE (RR = 0.39; 95% CI: 0.26, 0.59)
Pain response	Lysine acetylsalicylic acid vs. DHE (1 RCT)	Insufficient	Significant effect in favor of lysine acetylsalicylic acid; (RR = 1.92; 95% CI: 1.10, 3.36)
Change in pain-VAS	Chlorpromazine vs. DHE (1 RCT)	Insufficient	Significant effect in favor of chlorpromazine (MD = -40.0; -47.12, -32.88)
Headache relief	Chlorpromazine vs. DHE (1 RCT)	Insufficient	No significant difference between groups (RR = 1.44; 95% CI: 0.59, 3.56)

CI = confidence interval; DHE = dihydroergotamine; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

Triptans were compared with placebo in eight trials and with other active agents in six trials (Table 50). Sumatriptan was more effective than placebo for pain relief (moderate strength of evidence), and more effective than placebo for headache recurrence in the ED setting (low strength of evidence). Results were mixed for pain relief when triptans were compared with other active agents. Single trials compared triptans with neuroleptics, metoclopramide, trimethobenzamide, DHE, and ketorolac (insufficient strength of evidence). The mixed treatment analysis demonstrated that sumatriptan was similarly effective to orphan agents and other anti-nauseants, but less effective than opioids, NSAIDs, and metoclopramide (low strength of evidence). There was insufficient strength of evidence for headache recurrence when comparing triptans with other active agents.

Table 50. Summary of the strength of evidence for the effectiveness of triptans versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Headache relief at 60 min	Sumatriptan vs. placebo (4 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 3.03; 95% CI: 2.59, 3.54; I^2 = 0%)
Headache relief at 60 min	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant difference between groups (RR = 1.47; 95% CI: 0.90, 2.38)
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; I^2 = 21%)
Headache relief at 120 min	Almotriptan vs. placebo (1 RCT)	Insufficient	Significant effect in favor of almotriptan (RR = 1.65; 95% CI: 1.15, 2.36)
Headache relief at 30 min–VAS	Sumatriptan vs. placebo (2 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = -15.45; 95% CI: -19.49, -11.41; I^2 = 0%)
Headache relief at 60 min- VAS	Sumatriptan vs. placebo (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (MD = -25.0; 95% CI: -29.32, -20.68)
Headache relief at 120 min- VAS	Sumatriptan vs. placebo (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (MD = -30.70; 95% CI: -35.02, -26.38)
Pain free status	Sumatriptan vs. placebo (5 RCTs)	Moderate	Significant effect in favor of sumatriptan (RR = 4.73; 95% CI: 3.77, 5.94; I^2 = 0%)
Pain free status	Almotriptan vs. placebo (1 RCT)	Insufficient	No significant difference between groups (MD = 1.63; 95% CI: 0.85, 3.11)
Headache recurrence (24 hr; ED setting)	Sumatriptan vs. placebo (4 RCTs)	Low	Significant effect in favor of sumatriptan (RR = 0.72; 95% CI: 0.57, 0.90; I^2 = 23%)
Headache recurrence (24 hr; non- ED setting)	Sumatriptan vs. placebo (1 RCT)	Insufficient	Significant effect in favor of placebo (RR = 2.40; 95% CI: 1.45, 3.97)
Headache severity at discharge	Sumatriptan vs. placebo (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (MD = -0.80; 95% CI: -1.40, -0.20)
Change in pain (<2 hrs)–VAS	Metoclopramide vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = -9.0; 95% CI: -20.99, 2.99)
Change in pain intensity (24 hrs)-NRS	Metoclopramide vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 1.10; 95% CI: -0.60, 2.80)
Change in pain (<2 hrs)–-VAS	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 17.0; 95% CI: -0.08, 34.08)
Pain free response (1 hr)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.43; 95% CI: 0.13, 1.43)
Pain free response (2 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.67; 95% CI: 0.29, 1.52)
Pain free response (24 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.78; 95% CI: 0.36, 1.68)
Headache response (1 hr)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.88; 95% CI: 0.61, 1.26)
Headache response (2 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.94; 95% CI: 0.71, 1.25)

Table 50. Summary of the strength of evidence for the effectiveness of triptans versus placebo or an active treatment (Key Question 1) (continued)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Headache response (24 hrs)	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 1.13; 95% CI: 0.83, 1.55)
Change in pain intensity (24 hrs)-NRS	Trimethobenzamine + DPH vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 0.40; 95% CI: -1.50, 2.30)
Change in pain–VAS	Prochlorperazine + DPH vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of prochlorperazine (MD = -23.0; 95% CI: -35.5, -10.5)
Change in pain–VAS	Ketorolac vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of ketorolac (MD = -48.53; 95% CI: -65.54, -31.51)
Headache relief (1 hr)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (RR = 0.73; 95% CI: 0.61, 0.86)
Headache relief (2 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (RR = 0.86; 95% CI: 0.76, 0.96)
Headache relief (3 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 0.96; 95% CI: 0.88, 1.04)
Headache relief (4 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	No significant difference between groups (RR = 1.03; 95% CI: 0.93, 1.13)
Headache relief (24 hrs)	DHE vs. sumatriptan (1 RCT)	Insufficient	Significant effect in favor of DHE (RR = 1.17; 95% CI: 1.05, 1.30)
Headache recurrence	Sumatriptan vs. DHE (1 RCT)	Insufficient	Significant effect in favor of DHE (RR = 0.39; 95% CI: 0.26, 0.59)

CI = confidence interval; DHE = dihydroergotamine; DPH = diphenhydramine; ED = emergency department; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

$MgSO_4$ was compared with placebo in four trials and with other active agents in two trials (Table 51). $MgSO_4$ was more effective than placebo for pain relief (moderate strength of evidence) and headache recurrence (low strength of evidence). There was insufficient strength of evidence for pain relief and headache recurrence when comparing $MgSO_4$ with other active agents.

Table 51. Summary of the strength of evidence for the effectiveness of $MgSO_4$ versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain intensity–VAS	$MgSO_4$ vs. placebo (3 RCTs)	Moderate	Significant effect in favor of $MgSO_4$ (MD = -9.73; -16.75, -2.72; I^2 = 0%)
Pain reduction	$MgSO_4$ vs. placebo (2 RCTs)	Insufficient	No significant difference between groups (RR = 2.75; 95% CI: 0.20, 37.76; I^2 = 87%)
Headache recurrence	$MgSO_4$ vs. placebo (2 RCTs)	Low	No significant difference between groups (RR = 0.68; 95% CI: 0.29, 1.63; I^2 = 78%)
Headache response (60 min)	$MgSO_4$ vs. placebo (1 RCT)	Insufficient	Significant effect in favor of sumatriptan (RR = 2.78; 95% CI: 1.42, 5.44)
Pain intensity- VAS	Metoclopramide vs. $MgSO_4$ (1 RCT)	Insufficient	No significant difference between groups (MD = -5.0; 95% CI: -15.80, 5.80)
Headache recurrence	Metoclopramide vs. $MgSO_4$ (1 RCT)	Insufficient	No significant difference between groups (MD = 0.82; 95% CI: 0.51, 1.33)
Pain intensity- VAS	Prochlorperazine vs. MgSO4 (1 RCT)	Insufficient	Significant effect favors prochlorperazine (MD = -23.0; 95% CI: -44.67, -1.33)

CI = confidence interval; MD = mean difference; $MgSO_4$ = magnesium sulfate; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog scale

Antihistamines were compared with placebo in one trial (Table 52). There was insufficient strength of evidence for pain relief.

Table 52. Summary of the strength of evidence for the effectiveness of antihistamines versus placebo or an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Headache relief- VAS	Antihistamine vs. placebo (1 RCT)	Insufficient	No significant difference between groups (MD = -10.4; 95% CI: -28.18, 7.38)
Pain intensity–VAS	Nalbuphine vs hydoxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = -17.70; 95% CI: -36.85.14,1.45)
Pain intensity–VAS	Nalbuphine + hydroxyzine vs. hydroxyzine (1 RCT)	Insufficient	No significant difference between groups (MD = -1.90; 95% CI: -18.92, 15.12)

CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; VAS = visual analog scale

Eight RCTs compared eight different combination interventions with other active agents (Table 53). There was insufficient evidence to draw conclusions about the effectiveness of specific combination therapies for pain relief because single trials with low power investigated different pairs of interventions. The mixed treatment analysis demonstrated that DHE in combination with metoclopramide or neuroleptic agents was one of the more effective treatment options (low strength of evidence).

Table 53. Summary of the strength of evidence for the effectiveness of combination interventions versus an active treatment (Key Question 1)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Pain reduction–VAS	Metoclopramide + DHE vs. butorphanol (1 RCT)	Insufficient	No significant difference between groups (MD = -5.00; 95% CI: -19.98, 9.98)
Pain reduction–VAS	Metoclopramide + DHE vs. meperidine + hydroxyzine (1 RCT)	Insufficient	Significant effect in favor of metoclopramide + DHE; (MD = -22.00; 95%CI: -36.66, -7.34)
Pain reduction–VAS	Prochlorperazine + DHE vs. prochlorperazine (1 RCT)	Insufficient	No significant difference between groups (MD = 5.00; 95% CI: -18.96, 28.96)
Pain reduction–VAS	Metoclopramide + pethidine vs. metoclopramide (1 RCT)	Insufficient	No significant difference between groups (MD = 0.00; 95% CI: -8.47, 8.47)
Pain reduction–VAS	Metoclopramide + pethidine vs. pethidine (1 RCT)	Insufficient	Significantly favors metoclopramide + pethidine (MD = -10.0; 95% CI: -19.2, -0.79)
Pain reduction–VAS	Metoclopramide + $MgSO_4$ vs metoclopramide (1 RCT)	Insufficient	No significant difference between groups (MD = 16.00; 95% CI: -1.58, 33.58)
Pain reduction–VAS	Metoclopramide + DHE vs. valproate (1 RCT)	Insufficient	No significant difference between groups (RR = 1.10; 95%CI: 0.61,1.99)
Pain reduction–VAS	Metoclopramide + chlorpromazine vs. metoclopramide + sumatriptan (1 RCT)	Insufficient	No significant difference between groups (MD = 9.00; 95% CI: -4.04, 22.04)
Pain reduction–VAS	Metoclopramide + DHE vs. ketorolac (1 RCT)	Insufficient	Significant effect in favor of metoclopramide + DHE; (MD = -30.0; 95% CI: -57.72, -2.28)
Pain reduction–VAS	Metoclopramide + DHE vs metoclopramide + dexamethasone (1 RCT)	Insufficient	No significant difference between groups (RR = 0.95; 95% CI: 0.61, 1.49)

CI = confidence interval; DHE = dihydroergotamine; MD = mean difference; $MgSO_4$ = magnesium sulfate; RCT = randomized controlled trial; RR = risk ratio; VAS = visual analog 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 54). Of all patients with migraine, the subgroups most likely to benefit from dexamethasone are discussed under KQ 5 and 6.

Table 54. Summary of the strength of evidence for corticosteroids in the prevention of migraine relapse (Key Question 2)

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Headache recurrence (24-72 hr)	Dexamethasone 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)	Dexamethasone vs. placebo (1 RCT)	Insufficient	No significant difference (RR = 0.70; 95% CI: 0.43, 1.14)
Headache recurrence (30 days)	Dexamethasone vs. placebo (1 RCT)	Insufficient	No significant difference between groups (RR = 0.90; 95% CI: 0.58, 1.41)

CI = confidence interval; MD = mean difference; RCT = randomized controlled trial; RR = risk ratio

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 identify multiple studies testing the same medications and reporting common adverse effects (insufficient strength of evidence). We present a summary of adverse effects that provides an overall picture of which interventions had high rates of specific adverse effects.

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 or vomiting (11 percent), and chest symptoms (9 percent). There were few short-term side effects reported for opioids. While the risk of dependence and the association with headache relapse are important long-term side effects, these 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 patients; however, this is not surprising since these agents were all delivered subcutaneously. Chest symptoms (5 percent) were relatively infrequent. Due to the select populations in trials, the potential for adverse effects of the triptans might be higher, especially for patients with vascular risk factors. 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 indicates that metoclopramide and neuroleptics (e.g., prochlorperazine) are the anti-migraine agents most likely to cause these symptoms. Though other agents were associated with akathisia in the mixed treatment analysis, lack of precise diagnostic criteria may limit these results.

Clinicians commonly co-administer antihistamines (e.g., diphenhydramine, hydroxyzine) or anticholinergic agents (e.g., promethazine) with neuroleptics and metoclopramide to prevent akathsia. However, this review failed to identify convincing evidence to support this practice (Table 55). The small number of studies and small sample sizes of the included studies produced imprecise point estimates.

Table 55. Summary of strength of evidence for the development of akathisia when anticholinergic agents are added to metoclopramide or phenothiazines

Outcome	Comparison (# Studies)	Strength of Evidence	Summary
Akathisia	Metoclopramide+anticholinergic vs. phenothiazine+ anticholinergic (1 RCT)	Insufficient	No significant difference (OR = 1.50; 95% CI: 0.24, 9.52)
Akathisia	Prochlorperazine + DPH vs. prochlorperazine (1 RCT)	Insufficient	No significant difference (OR = 0.46; 95% CI: 0.17, 1.28)

DPH = diphenhydramine; OR = odds ratio; RCT = randomized controlled trial

Key Questions 5 and 6: Subpopulations

This review cannot comment on variability in response to anti-migraine treatment due to sex, race, or duration of headache because included studies often did not report results based on these variables. In one study where sex was reported as a subgroup, sex did not predict headache relapse.[21]

In one trial, dexamethasone was less effective at preventing relapse in patients who had more residual pain at discharge (VAS scores >2). In three trials,[19-21] dexamethasone was more effective in patients with prolonged headaches. In one published systematic review,[28] authors found that higher doses (≥15 mg) of IV dexamethasone were more effective than lower doses (<15 mg). These dose comparisons were repeated in this current review 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.[119] Research on practice patterns in adult patients with acute migraine headaches demonstrates considerable variation as well as the use of non-evidence based treatments.[16,120] Consequently, this CER is timely.

This review provides a comprehensive and up-to-date review of the available evidence. This includes evidence from placebo-controlled trials and head to head trials. Although there are published systematic reviews of DHE,[121] metoclopramide,[122] meperidine,[120] and systemic corticosteroids,[28] this CER 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 on 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.

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 CER were relatively homogenous. Most patients were females, and the mean age was generally between 30 and 40 years. Few studies reported on race or ethnicity; however, race was not an inclusion or exclusion criterion for any of the trials. Therefore, it would appear that these results are generalizable to most patients with acute migraine seen in similar EDs based on sex and age. Results may not apply to patients seen in EDs that serve more culturally diverse populations. It is unknown whether males respond

differently than females to the interventions included in this review. Similarly it is unknown whether the results of this review apply to older populations.

Headache severity on admission was reported in a variety of ways. In studies that reported a baseline VAS (mm), the mean scores ranged from 6.3 to 9.4, indicating moderate to severe headaches. In other studies, patients rated their headache as moderate or severe. Migraine headache was diagnosed using the International Headache Society criteria[2] in 61 percent of the studies; the remaining studies used other criteria (19 percent), or did not specify their criteria (20 percent). The median baseline headache severity (VAS = 8 mm) for studies that used other criteria or did not specify their criteria was the same as for studies that used the International Headache Society criteria. The results of this review may be generalizable to patients who present to the ED for treatment of moderate to severe acute migraine headache that has not responded to simple analgesics, and for whom IV agents are being contemplated.

The majority of trials took place in the ED (79 percent). For two comparisons more than 50 percent of the studies were conducted in a non-ED setting (NSAIDs versus placebo (2 of 2 studies) and $MgSO_4$ versus placebo (2 of 4 studies). The results for these interventions may not be generalizable to the ED setting.

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

Limitations of the Existing Evidence

The strength of the evidence was insufficient for the majority of outcomes across the head to head drug comparisons. This is primarily due to single, relatively small trials comparing pairs of active treatments. Where there were multiple trials, the strength of the evidence was low to moderate. These low grades were driven by moderate risk of bias within individual studies and a lack of consistency across 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 of the trials.

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. In addition, the therapeutic versus subtherapeutic dosing variation may limit some comparisons. This results in infrequent pooling and unclear direction of effect. For example, although there were multiple studies that investigated neuroleptic agents, use of different specific agents, doses, and comparators, as well as variable use of anticholinergic or antihistamine agents makes it difficult to draw conclusions about this class of drugs. Conversely, the corticosteroid data on relapse demonstrate the power of having consistent comparisons since the results are robust, precise, consistent, and generalizable.

There was inconsistency in reporting the outcomes from the studies included in this CER, which hampered efforts to provide 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 relative safety of these agents. For example, the definition of adverse effects, the

timing of assessment, and the scoring method used varied across studies. Still, serious or unexpected adverse effects were uncommon.

A small number of studies and overall small sample sizes contributed to imprecision. The nonsignificant differences between treatment comparisons reflect these weaknesses, and should not prompt conclusions about equivalence. Equivalence claims would require considerably larger sample sizes and 95 percent 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. We checked the data for inconsistency and found that the number of inconsistent nodes was small. Therefore, inconsistency was not a major concern. We also had categories "active combination agents" and "orphan agents" that do not distinguish between possible heterogeneous treatments within these groups.

In addition to the issues identified above, this CER has several limitations. Due to the small number of studies for each comparison we were unable to formally assess the potential for publication bias. Nonetheless, a comprehensive search of the published and 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 we did not contact authors to verify the methods used. Some studies may have been adequately conducted; however, the methods were poorly reported.

Future Research

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

- Since many of the trials demonstrated a benefit to treatment that exceeded placebo effect, placebo-controlled trials in this field should be replaced with comparative effectiveness research focusing on migraine-specific agents for the delivery of care.
- Since many clinicians provide combination agents when patients present with acute severe migraine headache, more efforts should be initiated to determine the effectiveness of combination agents compared with sequential administration of agents or monotherapy.
- Consensus on outcomes and outcome measures, including adverse effects, is needed to ensure consistency and comparability across future studies. Moreover, consensus on minimal clinically important differences is needed to guide study design and interpretation of results.
- Research in parenteral management of acute migraine is robust and ongoing. Consequently, updating this review should be a priority within 5 years.
- Future RCTs should investigate important subpopulations who may differentially respond to migraine treatment. This includes subgroup analyses by sex, race or ethnicity, age (e.g., older age groups), and duration of headache.
- Many trials included in this review were small and conducted in a single-center, which may have delayed the dissemination of evidence and knowledge more than necessary. A multi-centered acute migraine headache collaboration or consortium in emergency medicine would be an efficient method to answer the remaining important questions. The

results from this review support calls for well-powered multi-center trials using standardized methodologies.

- Future RCTs should seek to minimize risk of bias by blinding study participants and outcome assessors, adequately concealing allocation, and handling and reporting missing data appropriately.
- Trials should be designed and conducted to minimize bias where at all possible. Investigators may find tools such as the CONSORT statements[123] helpful in designing and reporting on RCTs.

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 for pain relief (VAS). Second, several treatments reported here provide insufficient evidence for continued use (e.g., lidocaine, anithistamines, sodium valproate). Third, systemic corticosteroids effectively prevent relapses, especially in patients with prolonged headaches. Finally, the list of adverse effects is extensive, albeit they vary among agents and classes of drugs. Overall, the effectiveness of therapies described here must be weighed against their side effects to derive a strategy for treating patients with this common disorder. While the evidence collated here is an important step, more research is required in order to identify the most effective and safest parenteral medication for acute migraine.

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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
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HT	5-hydroxytryptamine
hr	hour(s)
IQR	interquartile range
IV	intravenous
kg	kilogram(s)
MD	mean difference
mg	milligram(s)
$MgSO_4$	magnesium sulfate
ml	milliliter(s)
mm	millimeter(s)
min	minutes
NRCT	nonrandomized controlled trial
NSAIDs	nonsteroidal anti-inflammatory drug
OR	odds ratio
RCT	randomized controlled trial
RR	risk ratio
VAS	visual analogue scale

Appendix A. Search Strategies

Table A1. Acute migraine review - Ovid MEDLINE(R)

Version: OvidSP_UI03.04.00.105, SourceID 54178 **Years/issue searched**: 1948 to June Week 1 2011 **Search date:** June 13, 2011 **Limits:** "all adult (19 plus years)"; human **Results:** 209 Deduped: 196
1. Migraine Disorders/ 2. migraine with aura/ 3. migraine without aura/ 4. Headache/ 5. exp Headache Disorders/ 6. migrain$.mp. 7. (headach$ or head-ach$).tw. 8. (cephalgi$ or cephalalgi$).tw. 9. or/1-8 10. exp serotonin 5-HT1 receptor agonists/ 11. sumatript$.mp. 12. zolmitript$.mp. 13. rizatrip$.mp. 14. eletript$.mp. 15. naratript$.mp. 16. almotript$.mp. 17. frovatript$.mp. 18. exp ergot alkaloids/ 19. dihydroergotami$.mp. 20. DHE.tw. 21. ergotami$.mp. 22. exp analgesics, non-narcotic/ 23. acetaminophen.mp. 24. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).tw. 25. exp anti-inflammatory agents, non-steroidal/ 26. (NSAIA? or NSAID?).tw. 27. ((nonsteroidal or non-steroidal) adj anti-inflammator$).tw. 28. aspirin.mp. 29. (acetylsalicylic acid or ASA).tw. 30. (acetilsalicilico or acetilszalicilsav or acetylsalicyl$ or asetilsalisilik or asetyylisalisyylihappo or acetylosalicylowy).tw. 31. diclofen$.mp. 32. (diklofen$ or diclophen$).tw. 33. ibuprofen$.mp. 34. ibuprofeeni.tw. 35. (ketoprof$ or dexketoprofeno).mp. 36. ketorola$.mp. 37. naprox$.mp. 38. naprok$.tw. 39. exp analgesics, opioid/ 40. exp narcotics/ 41. morphine/ 42. (morphin* or morfiini* or morfin*).mp. 43. buprenorphin*.mp. 44. butorphanol$.mp. 45. butorfanol$.tw. 46. codein$.mp. 47. (kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).tw. 48. fentanyl.mp. 49. hydromorphon*.mp. 50. meperidin$.mp.

51. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).tw.
52. nalbuphin$.mp.
53. nalbufin$.tw.
54. tramadol$.mp.
55. propofol$.mp.
56. disoprofol.tw.
57. ketamin$.mp.
58. valproic acid/
59. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).tw.
60. exp antiemetics/
61. (antiemetic$ or anti-emetic$).tw.
62. haloperidol/
63. (haloperidol* or aloperidolo).mp.
64. Trimethobenzamide.mp.
65. exp Phenothiazines/
66. chlorpromazin$.mp.
67. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).tw.
68. promethazin$.mp.
69. (prometatsiini or prometazin or prometazina or promethazinum).tw.
70. methotrimeprazin$.mp.
71. (levomeproma$ or lewomepromazyny).tw.
72. prochlorperazin$.mp.
73. (chlormeprazine or prochlorpemazine or proklooriperatsiini or proklorperazin).tw.
74. ondansetron$.mp.
75. droperidol$.mp.
76. metoclopramid$.mp.
77. metoklopramid$.tw.
78. domperidon$.mp.
79. exp histamine h1 antagonists/
80. diphenhydramin$.mp.
81. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).tw.
82. dimenhydrinat$.mp.
83. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).tw.
84. butalbital$.mp.
85. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).tw.
86. Botulinum Toxins, Type A/
87. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).tw.
88. lidocain$.mp.
89. (lidokaiini or lidokain$ or lignocain$).tw.
90. xylocain$.tw.
91. oxygen.mp.
92. nitric oxide/ or nitrous oxide/
93. ((nitric or nitrous) adj oxide).tw.
94. magnesium sulfate/
95. (magnesium adj (sulfat$ or sulphat$)).tw.
96. drug therapy, combination/
97. drug combinations/
98. combined modality therapy/
99. placebo$.mp.
100. (pharmacologic adj manag$).tw.
101. (abortive adj therap$).tw.
102. or/10-101
103. cortisone/
104. (coritson* or kortison* or kortizon* or kortyzon*).mp.
105. exp glucocorticoids/
106. glucocorticoid?.tw.
107. (corticosteroid? or steroid$).tw.
108. betamethason$.mp.

109. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).tw.
110. (budesonid* or budezonid*).mp.
111. dexamethason$.mp.
112. (deksametason$ or desamethason$ or dexametason$ or dexametazon$ or hexadecadrol).tw.
113. hydrocortison$.mp.
114. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).tw.
115. methylprednisolon$.mp.
116. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).tw.
117. prednisolon$.mp.
118. (deltahydrocortisone or metacortandralone or prednizolon$).tw.
119. prednison$.mp.
120. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).tw.
121. triamcinolon$.mp.
122. (fluoxiprednisolonum or triamcynolon or triamsinoloni).tw.
123. or/103-122
124. or/10-122
125. Injections, Intramuscular/
126. Injections, Intravenous/
127. Injections, Subcutaneous/
128. Infusions, Intravenous/
129. Infusions, Parenteral/
130. (IM or intramuscular$ or intra-muscular$).tw.
131. (IV or intravenous$ or intra-venous$).tw.
132. (SC or subcutan$ or sub-cutan$ or sub-cu?).tw.
133. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).tw.
134. or/125-133
135. Emergency Treatment/
136. Emergency Service, Hospital/
137. Emergency Medical Services/
138. Emergencies/
139. Ambulatory Care Facilities/
140. Community Health Centers/
141. exp Outpatient Clinics, Hospital/
142. Community Health Services/
143. exp General Practice/
144. Primary Health Care/
145. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).tw.
146. ED?.tw.
147. ER?.tw.
148. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).tw.
149. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).tw.
150. (community adj2 (service? or care)).tw.
151. (primary adj2 care).tw.
152. (urgent adj2 care).tw.
153. ((pain or headache or head-ache or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).tw.
154. or/135-153
155. and/9,124,134,154
156. limit 155 to "all adult (19 plus years)"
157. exp animals/ not humans.sh.
158. 156 not 157
159. (comment or editorial or letter).pt.
160. 158 not 159
161. remove duplicates from 160
162. and/102,134
163. or/123,162
164. and/9,154,163
165. limit 164 to "all adult (19 plus years)"
166. 165 not 161

Table A2. Acute migraine review - EMBASE

Version: OvidSP_UI03.04.00.105, SourceID 54178
Years/issue searched: 1980 to 2011 Week 23
Search date: June 13, 2011
Limits: (adult <18 to 64 years> or aged <65+ years>)
Results: 480 Deduped: 329

1. exp migraine/
2. headache/
3. migrain$.mp.
4. (headach$ or head-ach$).tw.
5. (cephalgi$ or cephalalgi$).tw.
6. or/1-5
7. exp antimigraine agent/
8. exp serotonin agonist/
9. sumatript$.mp.
10. zolmitript$.mp.
11. rizatrip$.mp.
12. eletript$.mp.
13. naratript$.mp.
14. almotript$.mp.
15. frovatript$.mp.
16. ergot alkaloid/
17. dihydroergotami$.mp.
18. DHE.tw.
19. ergotami$.mp.
20. exp analgesic agent/
21. acetaminophen.mp.
22. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).tw.
23. exp nonsteroid antiinflammatory agent/
24. (NSAIA? or NSAID?).tw.
25. ((nonsteroidal or non-steroidal) adj anti-inflammator$).tw.
26. aspirin.mp.
27. (acetylsalicylic acid or ASA).tw.
28. (acetilsalicilico or acetilszalicilsav or acetylsalicyl$ or asetilsalisilik or asetyylisalisyylihappo or acetylosalicylowy).tw.
29. diclofen$.mp.
30. (diklofen$ or diclophen$).tw.
31. ibuprofen$.mp.
32. ibuprofeeni.tw.
33. (ketoprof$ or dexketoprofeno).mp.
34. ketorola$.mp.
35. naprox$.mp.
36. naprok$.tw.
37. exp narcotic agent/
38. exp opioid agonist/
39. butorphanol/
40. buprenorphin$.mp.
41. butorphanol$.mp.
42. butorfanol$.tw.
43. codein$.mp.
44. fentanyl.mp.
45. hydromorphon*.mp.
46. (kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).tw.
47. meperidin$.mp.
48. morphin*.mp.
49. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).tw.
50. nalbuphin$.mp.
51. nalbufin$.tw.
52. tramadol$.mp.
53. propofol$.mp.
54. disoprofol.tw.

55. ketamin$.mp.
56. valproic acid/
57. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).tw.
58. exp antiemetics/
59. exp antiemetic agent/
60. (antiemetic$ or anti-emetic$).tw.
61. exp trimethobenzamide/
62. trimethobenzamid*.mp.
63. haloperidol/
64. (haloperidol* or aloperidol*).mp.
65. exp phenothiazine derivative/
66. chlorpromazin$.mp.
67. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).tw.
68. promethazin$.mp.
69. (prometatsiini or prometazin or prometazina or promethazinum).tw.
70. methotrimeprazin$.mp.
71. (levomeproma$ or lewomepromazyny).tw.
72. prochlorperazin$.mp.
73. (chlormeprazine or prochlorpemazine or proklooriperatsiini or proklorperazin).tw.
74. ondansetron$.mp.
75. droperidol$.mp.
76. metoclopramid$.mp.
77. metoklopramid$.tw.
78. domperidon$.mp.
79. exp histamine H1 receptor antagonist/
80. diphenhydramin$.mp.
81. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).tw.
82. dimenhydrinat$.mp.
83. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).tw.
84. butalbital$.mp.
85. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).tw.
86. botulinum toxin A/
87. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).tw.
88. lidocain$.mp.
89. (lidokaiini or lidokain$ or lignocain$).tw.
90. xylocain$.tw.
91. oxygen.mp.
92. nitric oxide/ or nitrous oxide/
93. ((nitric or nitrous) adj oxide).tw.
94. magnesium sulfate/
95. (magnesium adj (sulfat$ or sulphat$)).tw.
96. adjuvant therapy/
97. "add on therapy"/
98. drug combination/
99. placebo/
100. placebo effect/
101. placebo$.mp.
102. (pharmacologic adj manag$).tw.
103. (abortive adj therap$).tw.
104. or/7-103
105. exp glucocorticoid/
106. glucocorticoid?.tw.
107. (corticosteroid? or steroid$).tw.
108. betamethason$.mp.
109. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).tw.
110. (budesonid* or budezonid*).mp.
111. (cortison* or kortison* or kortizon* or kortyzon*).mp.
112. dexamethason$.mp.

113. (deksametason$ or desamethason$ or dexametason$ or dexametazon$ or hexadecadrol).tw.
114. hydrocortison$.mp.
115. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).tw.
116. methylprednisolon$.mp.
117. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).tw.
118. prednisolon$.mp.
119. (deltahydrocortisone or metacortandralone or prednizolon$).tw.
120. prednison$.mp.
121. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).tw.
122. triamcinolon$.mp.
123. (fluoxiprednisolonum or triamcynolon or triamsinoloni).tw.
124. or/105-123
125. or/7-123
126. intramuscular drug administration/
127. intravenous drug administration/
128. subcutaneous drug administration/
129. parenteral drug administration/
130. (IM or intramuscular$ or intra-muscular$).tw.
131. (IV or intravenous$ or intra-venous$).tw.
132. (SC or subcutan$ or sub-cutan$ or sub-cu?).tw.
133. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).tw.
134. or/126-133
135. emergency treatment/
136. emergency care/
137. emergency health service/
138. emergency/
139. health care facility/
140. health center/
141. health care delivery/
142. aftercare/
143. ambulatory care/
144. community care/
145. primary health care/
146. pain clinic/
147. general practice/
148. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).tw.
149. ED?.tw.
150. ER?.tw.
151. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).tw.
152. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).tw.
153. (community adj2 (service? or care)).tw.
154. (primary adj2 care).tw.
155. (urgent adj2 care).tw.
156. ((pain or headache or head-ache or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).tw.
157. or/135-156
158. and/6,125,134,157
159. limit 158 to adult <18 to 64 years>
160. limit 158 to aged <65+ years>
161. or/159-160
162. (animal not (animal and human)).sh.
163. 161 not 162
164. (editorial or letter or note).pt.
165. 163 not 164
166. remove duplicates from 165
167. and/104,134
168. or/124,167
169. and/6,157,168
170. limit 169 to adult <18 to 64 years>
171. limit 169 to aged <65+ years>

172. or/170-171
173. remove duplicates from 172
174. 173 not 166

Table A3. Acute migraine review - EBM Reviews - Cochrane Central Register of Controlled Trials

Version: OvidSP_UI03.04.00.105, SourceID 54178
Years/issue searched: 1st Quarter 2011
Search date: June 13, 2011
Limits: MEDLINE or EMBASE records
Results: 4 De-duped: 2

1. Migraine Disorders/
2. migraine with aura/
3. migraine without aura/
4. Headache/
5. exp Headache Disorders/
6. migrain$.mp.
7. (headach$ or head-ach$).tw.
8. (cephalgi$ or cephalalgi$).tw.
9. or/1-8
10. exp Serotonin Agonists/
11. sumatript$.mp.
12. zolmitript$.mp.
13. rizatrip$.mp.
14. eletript$.mp.
15. naratript$.mp.
16. almotript$.mp.
17. frovatript$.mp.
18. exp ergot alkaloids/
19. dihydroergotami$.mp.
20. DHE.tw.
21. ergotami$.mp.
22. exp analgesics, non-narcotic/
23. acetaminophen.mp.
24. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).tw.
25. exp anti-inflammatory agents, non-steroidal/
26. (NSAIA? or NSAID?).tw.
27. ((nonsteroidal or non-steroidal) adj anti-inflammator$).tw.
28. aspirin.mp.
29. (acetylsalicylic acid or ASA).tw.
30. (acetilsalicilico or acetilszalicilsav or acetylsalicyl$ or asetilsalisilik or asetyylisalisyylihappo or acetylosalicylowy).tw.
31. diclofen$.mp.
32. (diklofen$ or diclophen$).tw.
33. ibuprofen$.mp.
34. ibuprofeeni.tw.
35. (ketoprof$ or dexketoprofeno).mp.
36. ketorola$.mp.
37. naprox$.mp.
38. naprok$.tw.
39. exp analgesics, opioid/
40. exp narcotics/
41. morphine/
42. (morphin* or morfiini* or morfin*).mp.
43. buprenorphin*.mp.
44. butorphanol$.mp.
45. butorfanol$.tw.
46. codein$.mp.
47. (kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).tw.
48. fentanyl.mp.
49. hydromorphon*.mp.
50. meperidin$.mp.
51. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).tw.
52. nalbuphin$.mp.
53. nalbufin$.tw.
54. tramadol$.mp.

55. propofol$.mp.
56. disoprofol.tw.
57. ketamin$.mp.
58. valproic acid/
59. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).tw.
60. exp antiemetics/
61. (antiemetic$ or anti-emetic$).mp.
62. haloperidol/
63. (haloperidol* or aloperidolo).mp.
64. Trimethobenzamide.mp.
65. exp Phenothiazines/
66. chlorpromazin$.mp.
67. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).tw.
68. promethazin$.mp.
69. (prometatsiini or prometazin or prometazina or promethazinum).tw.
70. methotrimeprazin$.mp.
71. (levomeproma$ or lewomepromazyny).tw.
72. prochlorperazin$.mp.
73. (chlormeprazine or prochlorpemazine or proklooriperatsiini or proklorperazin).tw.
74. ondansetron$.mp.
75. droperidol$.mp.
76. metoclopramid$.mp.
77. metoklopramid$.tw.
78. domperidon$.mp.
79. exp histamine h1 antagonists/
80. diphenhydramin$.mp.
81. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).tw.
82. dimenhydrinat$.mp.
83. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).tw.
84. butalbital$.mp.
85. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).tw.
86. Botulinum Toxin Type A/
87. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).tw.
88. lidocain$.mp.
89. (lidokaiini or lidokain$ or lignocain$).tw.
90. xylocain$.tw.
91. oxygen.mp.
92. nitric oxide/ or nitrous oxide/
93. ((nitric or nitrous) adj oxide).tw.
94. magnesium sulfate/
95. (magnesium adj (sulfat$ or sulphat$)).tw.
96. drug therapy, combination/
97. drug combinations/
98. combined modality therapy/
99. placebo$.mp.
100. (pharmacologic adj manag$).tw.
101. (abortive adj therap$).tw.
102. or/10-101
103. cortisone/
104. (coritson* or kortison* or kortizon* or kortyzon*).mp.
105. exp glucocorticoids/
106. glucocorticoid?.tw.
107. (corticosteroid? or steroid$).tw.
108. betamethason$.mp.
109. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).tw.
110. (budesonid* or budezonid*).mp.
111. dexamethason$.mp.
112. (deksametason$ or desamethason$ or dexametason$ or dexametazon$ or hexadecadrol).tw.

113. hydrocortison$.mp.
114. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).tw.
115. methylprednisolon$.mp.
116. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).tw.
117. prednisolon$.mp.
118. (deltahydrocortisone or metacortandralone or prednizolon$).tw.
119. prednison$.mp.
120. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).tw.
121. triamcinolon$.mp.
122. (fluoxiprednisolonum or triamcynolon or triamsinoloni).tw.
123. or/103-122
124. or/10-122
125. Injections, Intramuscular/
126. Injections, Intravenous/
127. Injections, Subcutaneous/
128. Infusions, Intravenous/
129. Infusions, Parenteral/
130. (IM or intramuscular$ or intra-muscular$).tw.
131. (IV or intravenous$ or intra-venous$).tw.
132. (SC or subcutan$ or sub-cutan$ or sub-cu?).tw.
133. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).tw.
134. or/125-133
135. Emergency Treatment/
136. Emergency Service, Hospital/
137. Emergency Medical Services/
138. Emergencies/
139. Ambulatory Care Facilities/
140. Community Health Centers/
141. exp Outpatient Clinics, Hospital/
142. Community Health Services/
143. Family Practice/
144. Primary Health Care/
145. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).tw.
146. ED?.tw.
147. ER?.tw.
148. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).tw.
149. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).tw.
150. (community adj2 (service? or care)).tw.
151. (primary adj2 care).tw.
152. (urgent adj2 care).tw.
153. ((pain or headache or head-ache or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).tw.
154. or/135-153
155. and/9,124,134,154
156. limit 155 to (medline records or embase records)
157. 155 not 156
158. and/102,134
159. or/123,158
160. and/9,154,159
161. limit 160 to medline records
162. limit 160 to embase records
163. or/161-162
164. 160 not 163
165. 157 or 164

Table A4. Acute migraine review - EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 2011 (CDSR)

EBM Reviews - Database of Abstracts of Reviews of Effects 2nd Quarter 2011 (DARE)
Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations April 29, 2011
PASCAL 1984 to 2011 Week 26
International Pharmaceutical Abstracts 1970 to March 2011 (IPA)
Version: OvidSP_UI03.04.00.105, SourceID 54178
Search date: 30.06.2011
Number of results:

Database	Results	De-duped
CDSR	262	260
DARE	15	15
In-Process	20	13
Pascal	122	20
IPA	41	25

Table A5. Acute Migraine review - 4 CDSR, DARE, MEDLINE In-Process, PASCAL, IPA

1. migrain$.mp.
2. (headach$ or head-ach$).mp.
3. (cephalgi$ or cephalalgi$).mp.
4. or/1-3
5. (serotonin adj2 agonist?).mp.
6. sumatript$.mp.
7. zolmitript$.mp.
8. rizatrip$.mp.
9. eletript$.mp.
10. naratript$.mp.
11. almotript$.mp.
12. frovatript$.mp.
13. ergot alkaloid?.mp.
14. dihydroergotami$.mp.
15. DHE.mp.
16. ergotami$.mp.
17. analgesic?.mp.
18. acetaminophen.mp.
19. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).mp.
20. (NSAIA? or NSAID?).mp.
21. ((nonsteroidal or non-steroidal) adj anti-inflammator$).mp.
22. aspirin.mp.
23. (acetylsalicylic acid or ASA).mp.
24. (acetilsalicilico or acetilszalicilsav or acetylsalicyl$ or asetilsalisilik or asetyylisalisyylihappo or acetylosalicylowy).mp.
25. diclofen$.mp.
26. (diklofen$ or diclophen$).mp.
27. ibuprofen$.mp.
28. ibuprofeeni.mp.
29. (ketoprof$ or dexketoprofeno).mp.
30. ketorola$.mp.
31. naprox$.mp.
32. naprok$.mp.
33. narcotic?.mp.
34. (morphin* or morfiini* or morfin*).mp.
35. buprenorphin*.mp.
36. butorphanol$.mp.
37. butorfanol$.mp.
38. codein$.mp.
39. (kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).mp.
40. fentanyl.mp.
41. hydromorphon*.mp.
42. meperidin$.mp.
43. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).mp.
44. nalbuphin$.mp.
45. nalbufin$.mp.
46. tramadol$.mp.
47. propofol$.mp.
48. disoprofol.mp.
49. ketamin$.mp.
50. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).mp.
51. (antiemetic$ or anti-emetic$).mp.
52. (haloperidol* or aloperidolo).mp.
53. Trimethobenzamide.mp.
54. phenothiazin$.mp.
55. chlorpromazin$.mp.
56. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).mp.

57. promethazin$.mp.
58. (prometatsiini or prometazin$).mp.
59. methotrimeprazin$.mp.
60. (levomeproma$ or lewomepromazyny).mp.
61. prochlorperazin$.mp.
62. (chlormeprazine or prochlorpemazine or proklooriperatsiini or proklorperazin).mp.
63. ondansetron$.mp.
64. droperidol$.mp.
65. metoclopramid$.mp.
66. metoklopramid$.mp.
67. domperidon$.mp.
68. (antihistamin$ or anti-histamin$).mp.
69. diphenhydramin$.mp.
70. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).mp.
71. dimenhydrinat$.mp.
72. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).mp.
73. butalbital$.mp.
74. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).mp.
75. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).mp.
76. lidocain$.mp.
77. (lidokaiini or lidokain$ or lignocain$).mp.
78. xylocain$.mp.
79. oxygen.mp.
80. ((nitric or nitrous) adj oxide).mp.
81. (magnesium adj (sulfat$ or sulphat$)).mp.
82. (drug adj2 combination?).mp.
83. (combin? adj2 (therap$ or treatment?)).mp.
84. placebo$.mp.
85. (pharmacologic adj manag$).mp.
86. (abortive adj therap$).mp.
87. or/5-86
88. (coritson* or kortison* or kortizon* or kortyzon*).mp.
89. glucocorticoid?.mp.
90. (corticosteroid? or steroid$).mp.
91. betamethason$.mp.
92. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).mp.
93. (budesonid* or budezonid*).mp.
94. dexamethason$.mp.
95. (deksametason$ or desamethason$ or dexametason$ or dexametazon$ or hexadecadrol).mp.
96. hydrocortison$.mp.
97. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).mp.
98. methylprednisolon$.mp.
99. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).mp.
100. prednisolon$.mp.
101. (deltahydrocortisone or metacortandralone or prednizolon$).mp.
102. prednison$.mp.
103. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).mp.
104. triamcinolon$.mp.
105. (fluoxiprednisolonum or triamcynolon or triamsinoloni).mp.
106. or/88-105
107. or/5-105
108. (IM or intramuscular$ or intra-muscular$).mp.
109. (IV or intravenous$ or intra-venous$).mp.
110. (SC or subcutan$ or sub-cutan$ or sub-cu?).mp.
111. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).mp.
112. or/108-111
113. ((family or general) adj2 practice?).mp.
114. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).mp.
115. ED?.mp.

116. ER?.mp.
117. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).mp.
118. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).mp.
119. (community adj2 (service? or care)).mp.
120. (primary adj2 care).mp.
121. (urgent adj2 care).mp.
122. ((pain or headache or head-ache or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).mp.
123. or/113-122
124. and/4,107,112,123
125. and/87,112
126. or/106,125
127. and/4,123,126
128. 127 not 124

Table A6. Acute migraine review - CINAHL Plus with Full Text EBSCOhost

Years/issue searched: 1937 to the present
Search date: June 14, 2011
Number of results: 131
Limiters/Expanders: Search modes - Find all my search terms
Last Run Via: Interface - EBSCOhost
Search Screen - Advanced Search

Limiters and Last Run Via apply to all lines of search strategy

ID	Search	Hits
S144	S7 and S107 and S120 and S143	134
S143	S121 or S122 or S123 or S124 or S125 or S126 or S127 or S128 or S129 or S130 or S131 or S132 or S133 or S134 or S135 or S136 or S137 or S138 or S139 or S140 or S141 or S142	493262
S142	AB urgent N2 care	370
S141	AB primary N2 care	22446
S140	AB community N2 service* or AB community N2 care	7769
S139	AB walk-in N2 clinic* or AB walk-in N2 care or AB walk-in N2 centre* or AB walk-in N2 center* or AB walk-in N2 service* or AB walk-in N2 unit*	149
S138	AB walkin N2 clinic* or AB walkin N2 care or AB walkin N2 centre* or AB walkin N2 center* or AB walkin N2 service* or AB walkin N2 unit*	1
S137	AB pain N2 clinic* or AB pain N2 care or AB pain N2 centre* or AB pain N2 center* or AB pain N2 service* or AB pain N2 unit*	3528
S136	AB outpatient N2 clinic* or AB outpatient N2 care or AB outpatient N2 centre* or AB outpatient N2 center* or AB outpatient N2 service*	5883
S135	AB out-patient N2 clinic* or AB out-patient N2 care or AB out-patient N2 centre* or AB out-patient N2 center* or AB out-patient N2 service*	385
S134	AB ambulatory N2 clinic* or AB ambulatory N2 care or AB ambulatory N2 centre* or AB ambulatory N2 center* or AB ambulatory N2 service*	2236
S133	AB ED* or AB ER*	165428
S132	AB emergenc* N3 department* or AB emergenc* N3 ward* or AB emergenc* N3 service* or AB emergenc* N3 unit* or AB emergenc* N3 room* or AB emergenc* N3 hospital* or AB emergenc* N3 care or AB emergenc* N3 medicin* or AB emergenc* N3 treatment* or AB emergenc* N3 admission*	19812
S131	AB emerg N3 department* or AB emerg N3 ward* or AB emerg N3 service* or AB emerg N3 unit* or AB emerg N3 room* or AB emerg N3 hospital* or AB emerg N3 care or AB emerg N3 medicin* or AB emerg N3 treatment* or AB emerg N3 admission*	3
S130	(MH "Primary Health Care")	28246
S129	(MH "Family Practice")	13482
S128	(MH "Community Health Services+")	233566
S127	(MH "Outpatient Service")	4335
S126	(MH "Community Health Centers")	2384
S125	(MH "Ambulatory Care Facilities+")	8334
S124	(MH "Emergencies+")	6168
S123	(MH "Emergency Medical Services+")	48860
S122	(MH "Emergency Service+")	24429
S121	(MH "Emergency Care+")	22162
S120	S108 or S109 or S110 or S111 or S112 or S114 or S115 or S116 or S118 or S119	40259

S119	AB parenteral* N2 inject* or AB parenteral* N2 administ* or AB parenteral* N2 therap* or AB parenteral* N2 treatment*	619
S118	AB subcutan* or sub-cutan* or sub-cu*	4863
S117	AB SC	0
S116	AB intravenous* or AB intra-venous*	12662
S115	AB IV	11881
S114	AB intramuscular* or AB intra-muscular*	1796
S113	AB IM	0
S112	(MH "Infusions, Parenteral+")	7435
S111	(MH "Infusions, Intravenous")	5081
S110	(MH "Injections, Subcutaneous+")	2038
S109	(MH "Injections, Intravenous")	2943
S108	(MH "Injections, Intramuscular+")	2165
S107	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105 or S106	154362
S106	S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105	31569
S105	AB fluoxiprednisolonum or triamcynolon or triamsinoloni	0
S104	AB Triamcinolon*	242
S103	AB deltacortisone or deltadehydrocortisone or metacortandracin or prednizon*	0
S102	AB prednison*	969
S101	AB deltahydrocortisone or metacortandralone or prednizolon*	1
S100	AB prednisolon*	570
S99	AB meilprednizolon or methyl-prednisolon* or metilprednisolon* metilprednizolonas or metylprednisolon or metyyliprednisoloni	24
S98	AB methylprednisolon*	487
S97	AB cortisol or hidrocortisona or hidrokortizon* or hydrocortisonum or hydrokortison* or hydrokortyzon	1988
S96	AB hydrocortison*	266
S95	AB deksametason* or desamethason* or dexametason* or dexametazon or dexamethason* or hexadecadrol	2598
S94	AB dexamethason*	1126
S93	AB beetametasoni or betadexamethasone or betametason* or betametazon* or flubenisolon*	0
S92	AB betamethason*	160
S91	AB corticosteroid* or steroid*	22376
S90	AB Glucocorticoid*	1114
S89	(MH "Glucocorticoids+")	6500
S88	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or	136950

	S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87	
S87	AB abortive N1 therap*	37
S86	AB pharmacologic N1 manag*	274
S85	AB Placebo*	18141
S84	(MH "Combined Modality Therapy+")	19321
S83	(MH "Drug Combinations+")	13149
S82	(MH "Drug Therapy, Combination+")	18454
S81	AB magnesium N1 sulfat* or AB magnesium N1 sulphat*	268
S80	(MH "Magnesium Sulfate")	742
S79	AB nitric N1 oxide or AB nitrous N1 oxide	3953
S78	(MH "Nitric Oxide") OR (MH "Nitrous Oxide")	5587
S77	AB oxygen	12572
S76	AB xylocain*	35
S75	AB lidokaiini or lidokain* or lignocain*	360
S74	AB lidocain*	974
S73	AB Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A	570
S72	(MH "Botulinum Toxins")	2471
S71	AB alisobumalum or allylbarbit* or butalbitaali or butalbitalum or itobarbital or tetrallobarbital	0
S70	AB butalbital*	15
S69	AB chloranautine or dimenhidrinat* or dimenhydramina or dimenhydrina* or diphenhydramin*	432
S68	AB dimenhydrinat*	16
S67	AB benzhydramin* or difenhidramin* or difenhydramiinihydrokloridi; difenhydramin* or dimedrolum	0
S66	AB diphenhydramin*	152
S65	(MH "Histamine H1 Antagonists+")	2181
S64	AB domperidon*	30
S63	AB metoklopramid*	0
S62	AB metoclopramid*	237
S61	AB droperidol* or haloperidol* or aloperidol*	963
S60	AB ondansetron*	226
S59	AB chlormeprazine or prochlorpemazine or prochlorperazin* or proklooriperatsiini or proklorperazin	148
S58	AB prochlorperazin*	65
S57	AB levomeproma* or lewomepromazyny	15
S56	AB methotrimeprazin*	11
S55	AB prometatsiini or prometazin or prometazina or promethazinum	0
S54	AB promethazin*	60
S53	AB klooripromatsiini* or klorpromazin* or aminazine or chlor#promaz*	345

S52	AB chlorpromazin*	151
S51	(MH "Antipsychotic Agents, Phenothiazine+")	639
S50	AB antiemetic* or AB anti-emetic*	672
S49	(MH "Antiemetics+")	8039
S48	AB acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat* or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra	1490
S47	(MH "Valproic Acid")	1100
S46	AB ketamin*	519
S45	AB disoprofol*	0
S44	AB propofol*	897
S43	AB tramadol*	283
S42	AB morphin* or hydromorphon*	2042
S41	AB nalbuphin* or nalbufin*	29
S40	AB pethidin* or petidiinihydrokloridi or petidin* or petidinhydroklorid or petydyny	83
S39	AB meperidin*	182
S38	AB kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether	1
S37	AB codein*	219
S36	AB buprenorphin* or fentanyl	3260
S35	AB butorphanol* or butorfanol*	33
S34	(MH "Narcotics+")	18946
S33	(MH "Analgesics, Opioid+")	16017
S32	AB naprok*	0
S31	AB naprox*	277
S30	AB ketorola*	175
S29	AB ketoprof* or dexketoprofeno	64
S28	AB ibuprofeeni	0
S27	AB ibuprofen*	573
S26	AB diklofen* or diclophen*	1
S25	AB diclofen*	391
S24	AB acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli	896
S23	AB Acetaminophen	885
S22	(MH "Analgesics, Nonnarcotic+")	21107
S21	(MH "Analgesics+")	24881
S20	AB ergotami*	97
S19	AB DHE	34
S18	AB dihydroergotami*	90
S17	(MH "Ergot Alkaloids+")	602

S16	AB frovatript*	47
S15	AB almotript*	75
S14	AB naratript*	74
S13	AB eletript*	57
S12	AB Rizatript*	104
S11	AB zolmitript*	99
S10	AB imitrex or AB sumavel or AB treximet	8
S9	AB Sumatript*	366
S8	(MH "Serotonin Agonists+")	1519
S7	S1 or S2 or S3 or S4 or S5 or S6	17206
S6	AB cephalgi* or AB cephalalgi*	137
S5	AB head-ach*	21
S4	AB headach*	7028
S3	AB migrain*	3551
S2	(MH "Headache+")	13608
S1	(MH "Migraine")	6959

Table A7. Acute migraine review - Academic Search Complete EBSCOhost

Years/issue searched: 1887 - present
Search date: June 14, 2011
Number of results: 201
Limiters/Expanders: Search modes - Find all my search terms
Last Run Via: Interface - EBSCOhost
Search Screen - Advanced Search

Limiters and Last Run Via apply to all lines of search strategy

ID	Search	Hits
S144	S7 and S107 and S120 and S143	135
S143	S121 or S122 or S123 or S124 or S125 or S126 or S127 or S128 or S129 or S130 or S131 or S132 or S133 or S134 or S135 or S136 or S137 or S138 or S139 or S140 or S141 or S142	2714291
S142	AB urgent N2 care	521
S141	AB primary N2 care	35500
S140	AB community N2 service* or AB community N2 care	20615
S139	AB walk-in N2 clinic* or AB walk-in N2 care or AB walk-in N2 centre* or AB walk-in N2 center* or AB walk-in N2 service* or AB walk-in N2 unit*	680
S138	AB walkin N2 clinic* or AB walkin N2 care or AB walkin N2 centre* or AB walkin N2 center* or AB walkin N2 service* or AB walkin N2 unit*	2
S137	AB pain N2 clinic* or AB pain N2 care or AB pain N2 centre* or AB pain N2 center* or AB pain N2 service* or AB pain N2 unit*	4131
S136	AB outpatient N2 clinic* or AB outpatient N2 care or AB outpatient N2 centre* or AB outpatient N2 center* or AB outpatient N2 service*	9904
S135	AB out-patient N2 clinic* or AB out-patient N2 care or AB out-patient N2 centre* or AB out-patient N2 center* or AB out-patient N2 service*	745
S134	AB ambulatory N2 clinic* or AB ambulatory N2 care or AB ambulatory N2 centre* or AB ambulatory N2 center* or AB ambulatory N2 service*	3072
S133	AB ED* or AB ER*	2624521
S132	AB emergenc* N3 department* or AB emergenc* N3 ward* or AB emergenc* N3 service* or AB emergenc* N3 unit* or AB emergenc* N3 room* or AB emergenc* N3 hospital* or AB emergenc* N3 care or AB emergenc* N3 medicin* or AB emergenc* N3 treatment* or AB emergenc* N3 admission*	33467
S131	AB emerg N3 department* or AB emerg N3 ward* or AB emerg N3 service* or AB emerg N3 unit* or AB emerg N3 room* or AB emerg N3 hospital* or AB emerg N3 care or AB emerg N3 medicin* or AB emerg N3 treatment* or AB emerg N3 admission*	1
S130	(MH "Primary Health Care")	4133
S129	(MH "Family Practice")	641
S128	(MH "Community Health Services+")	6005
S127	(MH "Outpatient Service")	3
S126	(MH "Community Health Centers")	35
S125	(MH "Ambulatory Care Facilities+")	5
S124	(MH "Emergencies+")	8184
S123	(MH "Emergency Medical Services+")	7795
S122	(MH "Emergency Service+")	83
S121	(MH "Emergency Care+")	135
S120	S108 or S109 or S110 or S111 or S112 or S114 or S115 or S116 or S118 or S119	165984

S119	AB parenteral* N2 inject* or AB parenteral* N2 administ* or AB parenteral* N2 therap* or AB parenteral* N2 treatment*	1520
S118	AB subcutan* or sub-cutan* or sub-cu*	39358
S117	AB SC	20657
S116	AB intravenous* or AB intra-venous*	45020
S115	AB IV	79308
S114	AB intramuscular* or AB intra-muscular*	8714
S113	AB IM	21615
S112	(MH "Infusions, Parenteral+")	2
S111	(MH "Infusions, Intravenous")	14
S110	(MH "Injections, Subcutaneous+")	1
S109	(MH "Injections, Intravenous")	971
S108	(MH "Injections, Intramuscular+")	989
S107	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87 or S88 or S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105 or S106	398992
S106	S89 or S90 or S91 or S92 or S93 or S94 or S95 or S96 or S97 or S98 or S99 or S100 or S101 or S102 or S103 or S104 or S105	100757
S105	AB fluoxiprednisolonum or triamcynolon or triamsinoloni	0
S104	AB Triamcinolon*	1650
S103	AB deltacortisone or deltadehydrocortisone or metacortandracin or prednizon*	13
S102	AB prednison*	4590
S101	AB deltahydrocortisone or metacortandralone or prednizolon*	31
S100	AB prednisolon*	4629
S99	AB meilprednizolon or methyl-prednisolon* or metilprednisolon* metilprednizolonas or metylprednisolon or metyyliprednisoloni	166
S98	AB methylprednisolon*	2956
S97	AB cortisol or hidrocortisona or hidrokortizon* or hydrocortisonum or hydrokortison* or hydrokortyzon	11184
S96	AB hydrocortison*	1904
S95	AB deksametason* or desamethason* or dexametason* or dexametazon or dexamethason* or hexadecadrol	9212
S94	AB dexamethason*	8664
S93	AB beetametasoni or betadexamethasone or betametason* or betametazon* or flubenisolon*	25
S92	AB betamethason*	958
S91	AB corticosteroid* or steroid*	67583
S90	AB Glucocorticoid*	11619
S89	(MH "Glucocorticoids+")	7869

S88	S8 or S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25 or S26 or S27 or S28 or S29 or S30 or S31 or S32 or S33 or S34 or S35 or S36 or S37 or S38 or S39 or S40 or S41 or S42 or S43 or S44 or S45 or S46 or S47 or S48 or S49 or S50 or S51 or S52 or S53 or S54 or S55 or S56 or S57 or S58 or S59 or S60 or S61 or S62 or S63 or S64 or S65 or S66 or S67 or S68 or S69 or S70 or S71 or S72 or S73 or S74 or S75 or S76 or S77 or S78 or S79 or S80 or S81 or S82 or S83 or S84 or S85 or S86 or S87	306838
S87	AB abortive N1 therap*	27
S86	AB pharmacologic N1 manag*	205
S85	AB Placebo*	44372
S84	(MH "Combined Modality Therapy+")	977
S83	(MH "Drug Combinations+")	49
S82	(MH "Drug Therapy, Combination+")	26
S81	AB magnesium N1 sulfat* or AB magnesium N1 sulphat*	1169
S80	(MH "Magnesium Sulfate")	636
S79	AB nitric N1 oxide or AB nitrous N1 oxide	41479
S78	(MH "Nitric Oxide") OR (MH "Nitrous Oxide")	34305
S77	AB oxygen	162547
S76	AB xylocain*	121
S75	AB lidokaiini or lidokain* or lignocain*	460
S74	AB lidocain*	3360
S73	AB Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A	1681
S72	(MH "Botulinum Toxins")	23
S71	AB alisobumalum or allylbarbit* or butalbitaali or butalbitalum or itobarbital or tetrallobarbital	0
S70	AB butalbital*	44
S69	AB chloranautine or dimenhidrinat* or dimenhydramina or dimenhydrina* or diphenhydramin*	744
S68	AB dimenhydrinat*	71
S67	AB benzhydramin* or difenhidramin* or difenhydramiinihydrokloridi; difenhydramin* or dimedrolum	5
S66	AB diphenhydramin*	628
S65	(MH "Histamine H1 Antagonists+")	7
S64	AB domperidon*	272
S63	AB metoklopramid*	3
S62	AB metoclopramid*	637
S61	AB droperidol* or haloperidol* or aloperidol*	3502
S60	AB ondansetron*	902
S59	AB chlormeprazine or prochlorpemazine or prochlorperazin* or proklooriperatsiini or proklorperazin	144
S58	AB prochlorperazin*	136
S57	AB levomeproma* or lewomepromazyny	76
S56	AB methotrimeprazin*	17
S55	AB prometatsiini or prometazin or prometazina or promethazinum	2
S54	AB promethazin*	349

S53	AB klooripromatsiini* or klorpromazin* or aminazine or chlor#promaz*	1201
S52	AB chlorpromazin*	1081
S51	(MH "Antipsychotic Agents, Phenothiazine+")	0
S50	AB antiemetic* or AB anti-emetic*	1303
S49	(MH "Antiemetics+")	616
S48	AB acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat* or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra	6534
S47	(MH "Valproic Acid")	2333
S46	AB ketamin*	2796
S45	AB disoprofol*	0
S44	AB propofol*	3418
S43	AB tramadol*	1125
S42	AB morphin* or hydromorphon*	9694
S41	AB nalbuphin* or nalbufin*	136
S40	AB pethidin* or petidiinihydrokloridi or petidin* or petidinhydroklorid or petydyny	279
S39	AB meperidin*	287
S38	AB kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether	15
S37	AB codein*	1008
S36	AB buprenorphin* or fentanyl	4414
S35	AB butorphanol* or butorfanol*	295
S34	(MH "Narcotics+")	3534
S33	(MH "Analgesics, Opioid+")	46
S32	AB naprok*	6
S31	AB naprox*	1749
S30	AB ketorola*	507
S29	AB ketoprof* or dexketoprofeno	935
S28	AB ibuprofeeni	0
S27	AB ibuprofen*	3530
S26	AB diklofen* or diclophen*	38
S25	AB diclofen*	2719
S24	AB acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli	3583
S23	AB Acetaminophen	3370
S22	(MH "Analgesics, Nonnarcotic+")	0
S21	(MH "Analgesics+")	8293
S20	AB ergotami*	273
S19	AB DHE	262
S18	AB dihydroergotami*	147

S17	(MH "Ergot Alkaloids+")	167
S16	AB frovatript*	89
S15	AB almotript*	154
S14	AB naratript*	148
S13	AB eletript*	130
S12	AB Rizatript*	249
S11	AB zolmitript*	262
S10	AB imitrex or AB sumavel or AB treximet	75
S9	AB Sumatript*	974
S8	(MH "Serotonin Agonists+")	453
S7	S1 or S2 or S3 or S4 or S5 or S6	26293
S6	AB cephalgi* or AB cephalalgi*	594
S5	AB head-ach*	52
S4	AB headach*	20700
S3	AB migrain*	10169
S2	(MH "Headache+")	9693
S1	(MH "Migraine")	8446

Table A8. Acute migraine review - PubMed

Years/issue searched: last 180 days **Search date:** May 9, 2011 **Number of results:** 22	
1.1.1	((((((((((migraine disorders[MeSH Terms])) OR (migraine with aura[MeSH Terms])) OR (migraine without aura[MeSH Terms])) OR (headache[MeSH Terms])) OR (headache disorders[MeSH Terms])) OR (migrain*[Text Word]) OR ((headache*[Text Word]) OR head-ache*[Text Word]) OR (((cephalgi*[Text Word])) OR cephalalgi*[Text Word])))) AND ((((((((((((injections, intramuscular[MeSH Terms])) OR (injections, intravenous[MeSH Terms])) OR (Injections, Subcutaneous[MeSH Terms])) OR (infusions, intravenous[MeSH Terms])) OR (infusions, parenteral[MeSH Terms])) OR (((IM[Text Word]) OR intramuscular*[Text Word]) OR intra-muscular*[Text Word])) OR (((IV[Text Word]) OR intravenous*[Text Word]) OR intra-venous*[Text Word])) OR ((((SC[Text Word]) OR subcultan*[Text Word]) OR sub-cutan*[Text Word]) OR sub-cu*[Text Word])) OR ((((parenteral* AND inject*[Text Word]) OR parenteral* AND administ*[Text Word]) OR parenteral* AND therap*[Text Word]) OR parenteral* AND treatment*[Text Word])))) AND ((((((((((Ergot alkaloids[MeSH Terms]) OR Dihydroergotami*[Text Word]) OR DHE[Text Word]) OR Ergotami*[Text Word])) OR ((((((((Serotonin 5-HT1 receptor agonists[MeSH Terms]) OR Sumatript*[Text Word]) OR Zolmitript*[Text Word]) OR Rizatript*[Text Word]) OR Eletript*[Text Word]) OR Naratript*[Text Word]) OR Almotript*[Text Word]) OR Frovatript*[Text Word])) OR ((valproic acid[MeSH Terms]) OR ((((((((((((((((((((acide valproique[Text Word]) OR acido dipropilacetico[Text Word]) OR acido valproico[Text Word]) OR acidum valproicum[Text Word]) OR dipropylacetic acid[Text Word]) OR DPA[Text Word]) OR kyselina valproova[Text Word]) OR natrii valproas[Text Word]) OR natrio valproatas[Text Word]) OR natriumvalproaatti[Text Word]) OR natriumvalproat[Text Word]) OR natrium-valproat[Text Word]) OR valproat*[Text Word]) OR valproic acid[Text Word]) OR valproiinihappo[Text Word]) OR valproik asit[Text Word]) OR valproine rugutis[Text Word]) OR valproinsav[Text Word]) OR valproinsyra[Text Word])) OR ((((((((((((((((((((((((((((((((((((((Analgesics, non-narcotic[MeSH terms]) OR Acetaminophen[Text Word]) OR acetaminofeno[Text Word]) OR acetominophen[Text Word]) OR apap[Text Word]) OR asetaminofen[Text Word]) OR paracetamol[Text Word]) OR paracetamolis[Text Word]) OR paracetamolum[Text Word]) OR parasetamol[Text Word]) OR parasetamoli[Text Word]) OR NSAIA*[Text Word]) OR NSAID*[Text Word]) OR nonsteroidal anti-inflammator*[Text Word]) OR non-steroidal anti-inflammator*[Text Word]) OR Aspirin[Text Word]) OR acetylsalicylic acid[Text Word]) OR ASA[Text Word]) OR acetilsalicilico[Text Word]) OR acetilszalicilsav[Text Word]) OR acetylsalicyl*[Text Word]) OR asetilsalisilik[Text Word]) OR asetyylisalisyylihappo[Text Word]) OR acetylosalicylowy[Text Word]) OR Diclofen[Text Word]) OR diklofen*[Text Word]) OR diclophen*[Text Word]) OR Ibuprofen*[Text Word]) OR Ibuprofeeni[Text Word]) OR ketoprof*[Text Word]) OR dexketoprofeno[Text Word]) OR Ketorola*[Text Word]) OR Naprox*[Text Word]) OR Naprok*[Text Word])) OR (((((((histamine h1 antagonists[MeSH Terms]) OR diphenhydramin*[Text Word]) OR ((((benzhydramin*[Text Word]) OR difenhidramin*[Text Word]) OR difenhydramiinihydrokloridi[Text Word]) OR difenhydramin*[Text Word]) OR dimedrolum[Text Word]) OR dimenhydrinat*[Text Word]) OR ((((chloranautine[Text Word]) OR dimenhidrinat*[Text Word]) OR dimenhydramina[Text Word]) OR dimenhydrina*[Text Word]) OR diphenhydramin*[Text Word]) OR butalbital*[Text Word]) OR (((((alisobumalum[Text Word]) OR allylbarbit*[Text Word]) OR butalbitaali[Text Word]) OR butalbitalum[Text Word]) OR itobarbital[Text Word]) OR tetrallobarbital[Text Word])) OR (((((((nitric oxide[MeSH Terms]) OR nitrous oxide[MeSH Terms]) OR nitric oxide[Text Word]) OR nitrous oxide[Text Word]) OR Magnesium sulphate[MeSH Terms]) OR magnesium sulfat*[Text Word]) OR magnesium sulphat*[Text Word])) OR ((((((botulinum toxins, type a[MeSH Terms]) OR ((((((Botuliinitoksiini tyyppi A[Text Word]) OR Botulinum Toxin Type A[Text Word]) OR Botulinum A Toksini[Text Word]) OR Toxin typ A mot botulism[Text Word]) OR Toxina botulinica A[Text Word]) OR Toxine botulinique type A[Text Word]) OR Toxinum Botulinicum Typum A[Text Word]) OR Lidocain*[Text Word]) OR ((lidokaiini[Text Word]) OR lidokain*[Text Word]) OR lignocain*[Text Word]) OR Xylocain*[Text Word]) OR Oxygen[Text Word])) OR ((((((drug therapy, combination[MeSH Terms]) OR drug combinations[MeSH Terms]) OR combined modality therapy[MeSH Terms]) OR placebo*[Text Word]) OR pharmacologic manag*[Text Word]) OR abortive therap*[Text Word])))) OR ((((((((((((((((((glucocorticoids[MeSH Terms])) OR (glucocorticoid*[Text Word])) OR ((corticosteroid*[Text Word]) OR steroid*[Text Word])) OR (betamethason*[Text Word])) OR (((((beetametasoni[Text Word]) OR betadexamethasone[Text Word]) OR betametason*[Text Word]) OR betametazon*[Text Word]) OR flubenisolon*[Text Word])) OR (dexamethason*[Text Word])) OR ((((((deksametason*[Text Word]) OR desamethason*[Text Word]) OR dexametason*[Text Word]) OR dexametazon*[Text Word]) OR dexamethason*[Text Word]) OR hexadecadrol[Text Word])) OR (hydrocortison*[Text Word])) OR ((((((cortisol[Text Word]) OR hidrocortisona[Text Word]) OR hidrokortizon*[Text Word]) OR hydrocortisonum[Text Word]) OR hydrokortison*[Text Word]) OR hydrokortyzon[Text Word])) OR (methylprednisolon*[Text Word])) OR ((((((meilprednizolon[Text Word]) OR methyl-prednisolon*[Text Word]) OR metilprednisolon*[Text Word]) OR metilprednizolonas[Text Word]) OR metylprednisolon[Text Word]) OR metyyliprednisoloni[Text Word])) OR (prednisolon*[Text Word])) OR (((deltahydrocortisone[Text Word]) OR metacortandralone[Text Word]) OR prednizolon*[Text Word])) OR

(prednison[Text Word])) OR ((((deltacortisone[Text Word]) OR deltadehydrocortisone[Text Word]) OR metacortandracin[Text Word]) OR prednizon*[Text Word])) OR (triamcinolon[Text Word])) OR (((fluoxiprednisolonum[Text Word]) OR triamcynolon[Text Word]) OR triamsinoloni[Text Word]))))) AND ((((((((((((((((((((((((((emergency treatment[MeSH Terms])) OR (emergency service, hospital[MeSH Terms])) OR (emergency medical services[MeSH Terms])) OR (emergencies[MeSH Terms])) OR (ambulatory care facilities[MeSH Terms])) OR (community health centers[MeSH Terms])) OR (outpatient clinics, hospital[MeSH Terms])) OR (community health services[MeSH Terms])) OR (general practice[MeSH Terms])) OR (primary health care[MeSH Terms])) OR ((((((((((emerg department*[Text Word])) OR emerg ward*[Text Word]) OR emerg service*[Text Word]) OR emerg unit*[Text Word]) OR emerg room*[Text Word]) OR emerg hospital*[Text Word]) OR emerg care[Text Word]) OR emerg medicin*[Text Word]) OR emerg treatment*[Text Word]) OR emerg admission*[Text Word])) OR ((((((((((emergenc* AND department*[Text Word]) OR emergenc* AND ward*[Text Word]) OR emergenc* AND service*[Text Word]) OR emergenc* AND unit*[Text Word]) OR emergenc* AND room*[Text Word]) OR emergenc* AND hospital*[Text Word]) OR emergenc* AND care[Text Word]) OR emergenc* AND medicin*[Text Word]) OR emergenc* AND treatment*[Text Word]) OR emergenc* AND admission*[Text Word])) OR ((ED*[Text Word]) OR ER*[Text Word])) OR (((((ambulatory clinic*[Text Word]) OR ambulatory care[Text Word]) OR ambulatory center*[Text Word]) OR ambulatory centre*[Text Word]) OR ambulatory service*[Text Word])) OR (((((out-patient clinic*[Text Word]) OR out-patient care[Text Word]) OR out-patient center*[Text Word]) OR out-patient centre*[Text Word]) OR out-patient service*[Text Word])) OR (((((outpatient clinic*[Text Word]) OR outpatient care[Text Word]) OR outpatient center*[Text Word]) OR outpatient centre*[Text Word]) OR outpatient service*[Text Word])) OR ((community service*[Text Word]) OR community care[Text Word])) OR (primary care[Text Word])) OR (urgent care[Text Word])) OR (((((pain clinic*[Text Word]) OR pain center*[Text Word]) OR pain centre*[Text Word]) OR pain service*[Text Word]) OR pain unit*[Text Word])) OR (((((headache clinic*[Text Word]) OR headache center*[Text Word]) OR headache centre*[Text Word]) OR headache service*[Text Word]) OR headache unit*[Text Word])) OR (((((head-ache clinic*[Text Word]) OR head-ache center*[Text Word]) OR head-ache centre*[Text Word]) OR head-ache service*[Text Word]) OR head-ache unit*[Text Word])) OR (((((walkin clinic*[Text Word]) OR walkin center*[Text Word]) OR walkin centre*[Text Word]) OR walkin service*[Text Word]) OR walkin unit*[Text Word])) OR (((((walk-in clinic*[Text Word]) OR walk-in center*[Text Word]) OR walk-in centre*[Text Word]) OR walk-in service*[Text Word]) OR walk-in unit*[Text Word])))) AND (adult[MeSH] AND "last 180 days"[PDat])

Table A9. Acute migraine review - ISI Web of Knowledge[SM]

BIOSIS Previews® 1926-2011
Science Citation Index Expanded (SCI-EXPANDED) --1899-present
Conference Proceedings Citation Index- Science (CPCI-S) --1990-present
Search date: May 6, 2011
Number of results: BIOSIS: 476; SCI-EXPANDED: 671; CPCI-S: 51

ID	Search
#1	TS=(migrain* or headach* or cephalgi* or cephalalgi*)
#2	TS=(sumatript* or zolmitript* or rizatrip* or eletript* or naratript* or almotript* or frovatript* or ergot alkaloid* or dihydroergotami* or DHE or ergotami*)
#3	TS=(acetaminophen or paracetamol or NSAIA* or NSAID* or aspirin or acetylsalicylic acid or ASA or diclofen* or ibuprofen* or ketoprof* or ketorola* or naprox*)
#4	TS=(morphin* or buprenorphin* or butorphanol* or codein* or fentan* or hydromorphon* or meperidin* or pethidin* or nalbuphin* or tramadol* or propofol* or disoprofol or ketamin* or valproic or valproat*)
#5	TS=(phenothiazin* or chlorpromazin* or promethazin* or methotrimeprazin* or prochlorperazin* or ondansetron* or haloperidol* or aloperidolo* or droperidol* or metoclopramid* or domperidon* or diphenhydramin* or dimenhydrinat*)
#6	TS=(butalbital* or Botulinum Toxin Type A or lidocain* or xylocain* or oxygen or nitric oxide or nitrous oxide or magnesium sulfat* or magnesium sulphat*)
#7	TS=(glucocorticoid* or corticosteroid* or steroid* or betamethason* or dexamethason* or hydrocortison* or methylprednisolon* or prednisolon* or prednison* or triamcinolon*)
#8	TS=(IM or intramuscular* or IV or intravenous* or SC or subcutan* or parenteral or inject*)
#9	TS=((emerg or emergenc*) SAME (department* or ward* or service* or unit* or room* or hospital* or care or medicin* or treatment* or admission*))
#10	TS=(ED or ER)
#11	TS=((pain or headache or head-ache or walkin or walk-in or out-patient or outpatient) SAME (clinic* or centre* or center* or service* or unit*))
#12	#11 OR #10 OR #9
#13	#12 AND #8 AND #2 AND #1
#14	#12 AND #8 AND #3 AND #1
#15	#12 AND #8 AND #4 AND #1
#16	#12 AND #8 AND #5 AND #1
#17	#12 AND #8 AND #6 AND #1
#18	#12 AND #8 AND #7 AND #1
#19	#18 OR #17 OR #16 OR #15 OR #14 OR #13

Table A10. Acute migraine review - Dissertations & Theses

ProQuest Dissertations and Theses **Years/issue searched:** 1637-current **Search date:** May 1, 2011 **Number of results:** 13	**ProQuest Dissertations and Theses - UK & Ireland** **Years/issue searched:** 1716-current **Search date:** May 1, 2011 **Number of results**: 13
(migrain* or headach* or cephalgi* or cephalalgi*) AND (IM or intramuscular* or IV or intravenous* or SC or subcutan* or parenteral or inject*) AND (emergenc* or ED* or ER* or clinic or centre or center)	
Theses Canada Portal http://www.nlc-bnc.ca/thesescanada/ Searched: 01.05.2011 Results: 1 Searched "any keyword" field combinations of: migraine or headach or cephalgi or cephalalgi AND treatment or therapy AND emergency or ED or ER or clinic or centre or center Any keyword: migraine and treatment and emergency	
AMICUS No. 38061086 Richer, Lawrence. Practice variation in the treatment of children with migraine in the emergency department [microform] -- Ottawa : Library and Archives Canada = Bibliothèque et Archives Canada, 2010.	
National Library of Australia Trove http://trove.nla.gov.au/ Searched: 01.05.2011 Query: migraine emergency Limit: theses Results: 3	
1. The Role of Acceptance in Appraisal and Coping with Migraine Headaches Chiros, Christine E [Thesis : 2007] Keywords: acceptance; coping; migraine Available online 2. New Targets in Migraine Therapy; Nieuwe Behandelingstrategieën voor Migraine Van der Schueren, Bart [Thesis : 2009] Available online 3. Entwicklung und Habituation der P300 EKP-Komponente bei Kindern und Jugendlichen mit und ohne Migräne; Development and Habituation of the P300 ERP component with children and adolescents with and without migraine Pfüller, Ute [Thesis : 2004] Languages: German Keywords: p300; oddball paradigma; ereigniskorreliertes potenzial Available online	
OhioLINK ETDs http://etd.ohiolink.edu/ Searched: 01.05.2011 - scanning first 100 results – none relevant Query 1: migraine emergency (any field) Results: 1773 PhD (1087) MS (239) doctoral (1170) masters (575) Query 2: keywords:(migraine emergency) Results: 79	

Table A11. Acute migraine review - Meeting Abstracts & Proceedings

Years/issue searched: 1993 – present **Search date:** May 1, 2011 **Number of results:** ProceedingsFirst: 129; papers first: 6
(kw: migrain* or kw: headach* or kw: cephalgi* or kw: cephalalgi*) and (kw: sumatript* or kw: zolmitript* or kw: rizatrip* or kw: eletript* or kw: naratript* or kw: almotript* or kw: frovatript* or kw: dihydroergotami* or kw: DHE or kw: ergotami* or kw: acetaminophen or kw: paracetamol or kw: NSAIA* or kw: NSAID* or kw: aspirin or kw: acetylsalicylic or kw: ASA or kw: diclofen* or kw: ibuprofen* or kw: ketoprof* or kw: ketorola* or kw: naprox* or kw: butorphanol* or kw: buprenorphin* or kw: fentanyl or kw: codein* or kw: morhpin* or kw: hydromorphon* or kw: meperidin* or kw: pethidin* or kw: nalbuphin* or kw: tramadol* or kw: propofol* or kw: disoprofol or kw: ketamin* or kw: valproic or kw: valproat* or kw: phenothiazin* or kw: chlorpromazin* or kw: promethazin* or kw: methotrimeprazin* or kw: prochlorperazin* or kw: ondansetron* or kw: droperidol* or kw: haloperidol* or kw: aloperidol* or kw: metoclopramid* or kw: domperidon* or kw: diphenhydramin* or kw: dimenhydrinat* or kw: butalbital* or kw: Botulinum w2 Toxin or kw: lidocain* or kw: xylocain* or kw: oxygen or kw: nitric and kw: oxide or kw: nitrous and kw: oxide or (kw: magnesium and kw: sulfat*) or (kw: magnesium and kw: sulphat*) or kw: glucocorticoid* or kw: corticosteroid* or kw: steroid* or kw: betamethason* or kw: dexamethason* or kw: hydrocortison* or kw: methylprednisolon* or kw: prednisolon* or kw: prednison* or kw: triamcinolon*) and (kw: IM or kw: intramuscular* or kw: IV or kw: intravenous* or kw: SC or kw: subcutan* or kw: parenteral or kw: inject*) and (kw: emergenc* w2 department* or kw: emergenc* w2 ward* or kw: emergenc* w2 service* or kw: emergenc* w2 unit* or kw: emergenc* w2 room* or kw: emergenc* w2 hospital* or kw: emergenc* w2 care or kw: emergenc* w2 medicin* or kw: emergenc* w2 treatment* or kw: emergenc* w2 admission* or kw: ED* or kw: ER* or kw: walk-in w2 clinic* or kw: walk-in w2 centre* or kw: walk-in w2 center* or kw: walk-in w2 service* or kw: walk-in w2 unit* or kw: headache w2 clinic* or kw: headache w2 centre* or kw: headache w2 center* or kw: headache w2 service* or kw: headache w2 unit* or kw: out-patient w2 clinic* or kw: out-patient w2 centre* or kw: out-patient w2 center* or kw: out-patient w2 service* or kw: out-patient w2 unit* or kw: out-patient w2 clinic* or kw: out-patient w2 centre* or kw: out-patient w2 center* or kw: out-patient w2 service* or kw: out-patient w2 unit)

Table A12. Acute migraine review - NLM Gateway

Search date: May 1, 2011	
Query 1: emergency treatment adult migraine	
Results: 206 →no meeting abstracts	
Query 2: adult migraine emergency	
Results: 420 → no meeting abstracts	ClinicalTrials.gov: 18
Query 3: adult migraine emergency therapy	
Results: 285 → no meeting abstracts	ClinicalTrials.gov: 17

Table A13. Acute migraine review - Handsearching (Journals – supplements) Websites (Google and Exalead)

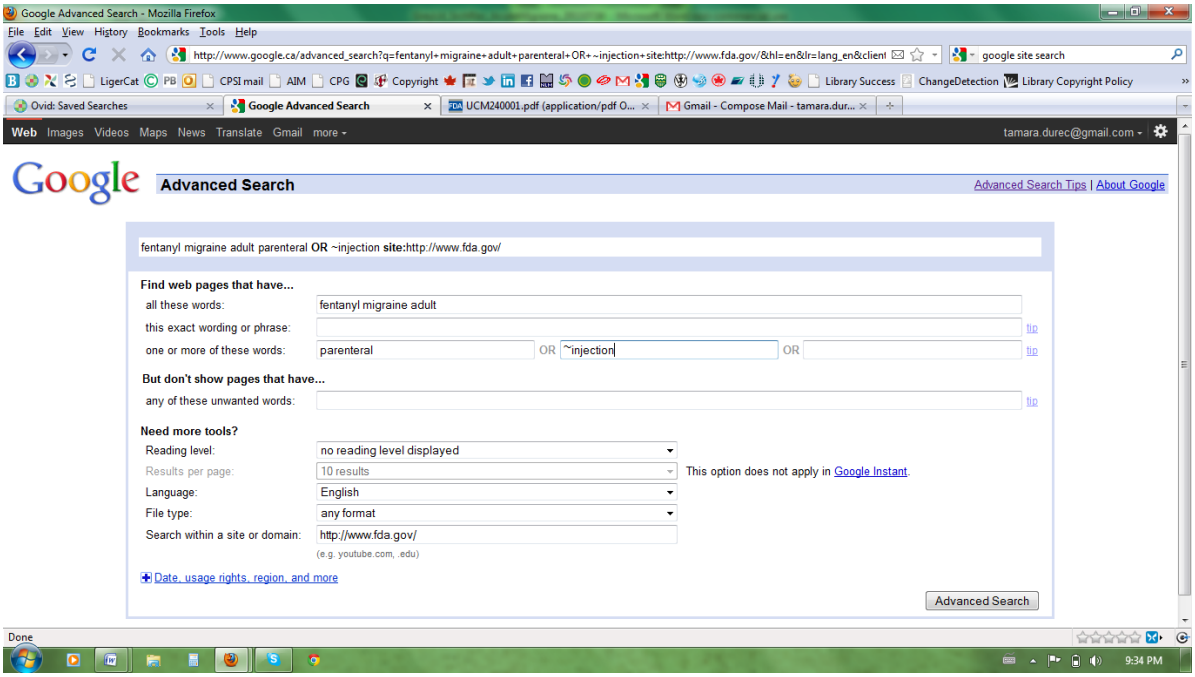
FDA.gov

http://www.fda.gov/

FDA site search based on highlighted terms

- Used Google advanced search, searching within a site or domain
  DRUG NAME parenteral injection migraine adult site:http://www.fda.gov/

-



Search terms taken from search below.
Searching only US spelling of generic drug name; no synonyms or acronyms
Search date: June 21, 2011-July 27, 2011

1. Migraine Disorders/
2. migraine with aura/
3. migraine without aura/
4. Headache/
5. exp Headache Disorders/
6. migrain$.mp.
7. (headach$ or head-ach$).tw.
8. (cephalgi$ or cephalalgi$).tw.
9. or/1-8
10. exp serotonin 5-HT1 receptor agonists/
11. sumatript$.mp.
12. zolmitript$.mp.
13. rizatrip$.mp.
14. eletript$.mp.
15. naratript$.mp.
16. almotript$.mp.
17. frovatript$.mp.
18. exp ergot alkaloids/
19. dihydroergotami$.mp.
20. DHE.tw.
21. ergotami$.mp.
22. exp analgesics, non-narcotic/
23. acetaminophen.mp.
24. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).tw.
25. exp anti-inflammatory agents, non-steroidal/

26. (NSAIA? or NSAID?).tw.
27. ((nonsteroidal or non-steroidal) adj anti-inflammator$).tw.
28. aspirin.mp.
29. (acetylsalicylic acid or ASA).tw.
30. (acetilsalicilico or acetilszalicilsav or acetylsalicyl$ or asetilsalisilik or asetyylisalisyylihappo or acetylosalicylowy).tw.
31. diclofen$.mp.
32. (diklofen$ or diclophen$).tw.
33. ibuprofen$.mp.
34. ibuprofeeni.tw.
35. (ketoprof$ or dexketoprofeno).mp.
36. ketorola$.mp.
37. naprox$.mp.
38. naprok$.tw.
39. exp analgesics, opioid/
40. exp narcotics/
41. morphine/
42. (morphin* or morfiini* or morfin*).mp.
43. buprenophin*.mp.
44. butorphanol$.mp.
45. butorfanol$.tw.
46. codein$.mp.
47. (kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).tw.
48. fentanyl.mp.
49. hydromorphon*.mp.
50. meperidin$.mp.
51. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).tw.
52. nalbuphin$.mp.
53. nalbufin$.tw.
54. tramadol$.mp.
55. propofol$.mp.
56. disoprofol.tw.
57. ketamin$.mp.
58. valproic acid/
59. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).tw.
60. exp antiemetics/
61. (antiemetic$ or anti-emetic$).tw.
62. haloperidol/
63. (haloperidol* or aloperidolo).mp.
64. Trimethobenzamide.mp.
65. exp Phenothiazines/
66. chlorpromazin$.mp.
67. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).tw.
68. promethazin$.mp.
69. (prometatsiini or prometazin or prometazina or promethazinum).tw.
70. methotrimeprazin$.mp.
71. (levomeproma$ or lewomepromazyny).tw.
72. prochlorperazin$.mp.
73. (chlormeprazine or prochlorpemazine or proklooriperatsiini or proklorperazin).tw.
74. ondansetron$.mp.
75. droperidol$.mp.
76. metoclopramid$.mp.
77. metoklopramid$.tw.
78. domperidon$.mp.
79. exp histamine h1 antagonists/
80. diphenhydramin$.mp.
81. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).tw.
82. dimenhydrinat$.mp.
83. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).tw.

84. butalbital$.mp.
85. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).tw.
86. Botulinum Toxins, Type A/
87. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).tw.
88. lidocain$.mp.
89. (lidokaiini or lidokain$ or lignocain$).tw.
90. xylocain$.tw.
91. oxygen.mp.
92. nitric oxide/ or nitrous oxide/
93. ((nitric or nitrous) adj oxide).tw.
94. magnesium sulfate/
95. (magnesium adj (sulfat$ or sulphat$)).tw.
96. drug therapy, combination/
97. drug combinations/
98. combined modality therapy/
99. placebo$.mp.
100. (pharmacologic adj manag$).tw.
101. (abortive adj therap$).tw.
102. or/10-101
103. cortisone/
104. (coritson* or kortison* or kortizon* or kortyzon*).mp.
105. exp glucocorticoids/
106. glucocorticoid?.tw.
107. (corticosteroid? or steroid$).tw.
108. betamethason$.mp.
109. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).tw.
110. (budesonid* or budezonid*).mp.
111. dexamethason$.mp.
112. (deksametason$ or desamethason$ or dexametason$ or dexametazon$ or hexadecadrol).tw.
113. hydrocortison$.mp.
114. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).tw.
115. methylprednisolon$.mp.
116. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).tw.
117. prednisolon$.mp.
118. (deltahydrocortisone or metacortandralone or prednizolon$).tw.
119. prednison$.mp.
120. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).tw.
121. triamcinolon$.mp.
122. (fluoxiprednisolonum or triamcynolon or triamsinoloni).tw.
123. or/103-122
124. or/10-122
125. Injections, Intramuscular/
126. Injections, Intravenous/
127. Injections, Subcutaneous/
128. Infusions, Intravenous/
129. Infusions, Parenteral/
130. (IM or intramuscular$ or intra-muscular$).tw.
131. (IV or intravenous$ or intra-venous$).tw.
132. (SC or subcutan$ or sub-cutan$ or sub-cu?).tw.
133. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).tw.
134. or/125-133
135. Emergency Treatment/
136. Emergency Service, Hospital/
137. Emergency Medical Services/
138. Emergencies/
139. Ambulatory Care Facilities/
140. Community Health Centers/
141. exp Outpatient Clinics, Hospital/
142. Community Health Services/
143. exp General Practice/

144. Primary Health Care/
145. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).tw.
146. ED?.tw.
147. ER?.tw.
148. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).tw.
149. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).tw.
150. (community adj2 (service? or care)).tw.
151. (primary adj2 care).tw.
152. (urgent adj2 care).tw.
153. ((pain or headache or head-ache or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).tw.
154. or/135-153
155. and/9,124,134,154
156. limit 155 to "all adult (19 plus years)"
157. exp animals/ not humans.sh.
158. 156 not 157
159. (comment or editorial or letter).pt.
160. 158 not 159
161. remove duplicates from 160
162. and/102,134
163. or/123,162
164. and/9,154,163
165. limit 164 to "all adult (19 plus years)"
166. 165 not 161

Table A14. Acute migraine review - Cited Reference Search

Trials Registries

ClinicalTrials.gov
http://clinicaltrials.gov/
Searched: 01.05.2011
Limits: Adult, senior
Results: 7 Excel file: AcuteMigraineTrials_20110501
Query: emergency | acute migraine | Adult, Senior

***meta*Register of Controlled Trials (*m*RCT)**
http://www.controlled-trials.com/mrct/
Searched: 01.05.2011
Results: 79 Word file: AcuteMigraine_Trials_20110501 (p1-11)
Query: acute migraine

WHO International Clinical Trials Registry Platform (ICTRP)
http://www.who.int/ictrp/en/
Search portal: http://apps.who.int/trialsearch/
Results: Word file: AcuteMigraine_Trials _20110501 (p12
Query 1: Basic search: acute migraine AND emergency
Results: 4

Query 2: Advanced search: Condition: acute migraine; Recruitment status: ALL
Results: 9

CenterWatch – no longer freely accessible – see webpage on "Headaches"*
http://www.centerwatch.com/
Follow link: Drug Information > Drugs in Clinical Trials Database
Subscription Information: The Drugs in Clinical Trials Database is accessible only by subscription, which can be purchased in the CenterWatch Bookstore. **For a free trial, please contact tracy.lawton@centerwatch.com.**

***Home » Clinical Trials » Search Clinical Trials**
Parent Therapeutic Areas: Neurology
"H" Headaches (5)
http://www.centerwatch.com/clinical-trials/listings/studylist.aspx?CatID=388

Table A15. Results summary

Database	Dates Searched	Number of results: Before TEP call (May); After TEP call (June)	After Duplicate Removal
Medline <1948 to June Week 1 2011>	1948 to June 2011	152; 57	150; 46
Embase <1980 to 2011>	13 June 2011	283; 197	172; 157
EBM Reviews—CENTRAL (2nd Quarter 2011)	13 June 2011	4; 0	2; 0
EBM Reviews—CDSR (2005 to March 2011)	30 June 2011	182; 80	182; 78
EBM Reviews—DARE (2nd Quarter 2011)	30 June 2011	12; 3	12; 3
Medline In-Process & Other Non-Indexed Citations (30 June 2011)	30 June 2011	9; 11	6; 7
Pascal (1984 to 2011 Week 26)	30 June 2011	89; 33	12; 8
International Pharmaceutical Abstracts (1970 to June 2011)	30 June 2011	34; 7	20; 5
CINAHL Plus with Full Text (1937 to present)	14 June 2011	54; 77	43; 50
Academic Search Complete (1887 to present)	14 June 2011	87; 114	82; 39
PubMed (last 180 days)	14 June 2011	8; 14	8; 6
Biosis Previews (1926-2011)	5 June 2011	249; 230	94; 82
Science Index Expanded (1899 to present)	5 June 2011	466; 205	358; 149
Conference Proceedings Citation Index–Science (1990 to present)	5 June 2011	51; 0	1; 0
ProQuest Dissertations and Theses–Ireland (1637 to current) & UK (1716 to current)	1 May 2011	13; 0	13; 0
These Canada Portal	1 May 2011	1; 0	1; 0
National Library of Australia Trove	1 May 2011	3; 0	3; 0
OCLC Papers First (1993 to present)	1 May 2011	6; 0	6; 0
OCLC Proceedings First (1993 to present)	1 May 2011	129; 0	129; 0
Total results		**2858**	**1922**

Appendix B. Sample Forms

B.1. Inclusion Criteria Worksheet: Acute migraine review

Reviewer ID: **Date:** **/** **/2011** **Record ID:**

Criteria	Yes	No	UC
1. PUBLICATION TYPE no date restriction			
a. Report of primary research	☐	☐	☐
2. STUDY DESIGN			
a. Efficacy and effectiveness: RCTs and NRCTs	☐	☐	☐
b. Safety: RCTs, NRCTs, and prospective cohort studies	☐	☐	☐
3. POPULATION			
a. Adult patients (≥ 18 years) with severe acute migraine headache presenting to an ED or equivalent setting and receiving parenteral therapy	☐	☐	☐
4. INTERVENTION			
In-ED treatment: First-line parenteral (intravenous/intramuscular/ subcutaneous) interventions: a) Metoclopramide (Maxeran/Reglan); b) Dihydroergotamine (DHE); c) NSAIDs (ketorolac {Toradol}); d) Phenothiazines (chlorpromazine {Largactil}, prochlorperazine {Stematil}, droperidol); e) Magnesium sulphate (MgSO4); 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)	☐	☐	☐
5. COMPARATOR GROUP			
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.	☐	☐	☐
6. OUTCOME			
1. Pain relief/change in pain score (measured either as Visual Analog Score {VAS}, 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; 9. Adverse effects of intervention(s) (e.g. sedation/somnolence; dizziness; restless legs/ akathisia; anxiety; vomiting; chest symptoms, palpitations; skin flushing; other side effects)	☐	☐	☐

Comments

REVIEWER'S DECISION : **Include** ☐ **Exclude** ☐ **Unsure** ☐

FINAL DECISION: Include ☐ **Exclude** ☐ **Unsure** ☐

B.2. Data extraction form: Acute migraine review

1. Publication information and study characteristics

Study author:			Source of funding: industry ☐ government ☐ foundation ☐ other ☐ Conflict of interest reported: _____		
Country(ies): Language:	Year of publication:		Recruitment period _____		
Publication type Abstract ☐ Journal article ☐			Trial registration reported: ☐ No ☐ Yes, report number_____		
Trial characteristics			Number of Centers		
RCT ☐ NRCT	Individual randomization ☐	Cluster randomization ☐	Single centre ☐	Multicentre ☐ # of centres _____	

2. Population

In ED timepoints:	Post ED followup:	Diagnostic criteria: International Headache Society ☐ American Medical Association ☐ Patients present to ED complaining of migraine ☐ Other (describe) ☐
Inclusion criteria:		Exclusion criteria:
Primary outcome:		Secondary outcomes:

3. Baseline Characteristics

	Group 1	Group 2	Group 3	Group 4
Pts randomized (n)				
Pts analyzed (n)				
Pts completed (n)				
ITT described				
Proportion of females (x/N)				
Age (mean (SD))				
Age (median (IQR)				
Race/ethnicity				
Description of severity of migraine				
Description of medication taken prior to coming to				

ED				
Duration of headache prior to coming to ED				
Time since last migraine				
Time since last ED visit for migraine				
Mean headaches per month				

4. Intervention and comparisons

	Group 1	Group 2	Group 3	Group 4
Drug class (according ot protocol')				
Drug class of additional drug				
Drug treatment name				
Dose/dosage				
Route of administration				
Dose interval				
Frequency of intervention				
Duration fo treatment				
Co-interventions				
Description of rescue therapy				

4. Intervention and comparisons

	Group 1	Group 2	Group 3	Group 4
Drug class (according ot protocol')				
Drug class of additional drug				
Drug treatment name				
Dose/dosage				
Route of administration				
Dose interval				

Frequency of intervention				
Duration fo treatment				
Co-interventions				
Description of rescue therapy				

5. Outcomes

Outcome component	Extracted information
Primary outcome	
Scale on which primary outcome is measured	
Secondary outcome(s)	
Scale on which secondary outcome(s) is/are measured	
Timepoints measured in ED	
Timepoints measured post ED	
Description of adverse reactions	
Akathesia described separately	

6. Conclusions

	Extracted information
Description of significant difference in primary outcome	
Description of significant difference in secondary outcome(s)	
Brief summary of conclusions	

B.3. Risk of Bias: Acute migraine review

Cochrane Collaboration's tool for assessing risk of bias: Acute Migraine

Reviewer's initials: _____ Study ID: _____ Date (dd/mm/yy): _____

Domain	**Description**	**Review authors' judgment**	**Consensus (circle)**
Sequence generation		Was the allocation sequence adequately generated? YES / NO / UNCLEAR	YES NO UNCLEAR
Allocation concealment		Was allocation adequately concealed? YES / NO / UNCLEAR	YES NO UNCLEAR
Blinding of participants, personnel and outcome assessors,	Objective outcomes: Self-reported outcomes:	Was knowledge of the allocated intervention adequately prevented during the study? Objective: YES / NO / UNCLEAR Self-reported: YES / NO / UNCLEAR	Objective: YES NO UNCLEAR Self-reported: YES NO UNCLEAR
Incomplete outcome data, *Outcome:*	Objective outcomes: Self-reported outcomes:	Were incomplete outcome data adequately addressed? Objective: YES / NO / UNCLEAR Self-reported: YES / NO / UNCLEAR	Objective: YES NO UNCLEAR Self-reported: YES NO UNCLEAR
Selective outcome reporting		Are reports of the study free of suggestion of selective outcome reporting? YES / NO / UNCLEAR	YES NO UNCLEAR
Other sources of bias	Baseline imbalance: Funding:	Was the study apparently free of other problems that could put it at a high risk of bias? Baseline: YES / NO / UNCLEAR Funding: YES / NO / UNCLEAR	Baseline: YES NO UNCLEAR Funding: YES NO UNCLEAR
Overall risk of bias	Objective outcomes	HIGH / LOW / UNCLEAR	HIGH/ LOW/ UNCLEAR
	Self-reported outcomes	HIGH / LOW / UNCLEAR	HIGH/ LOW/ UNCLEAR

Appendix C. Excluded Studies

157 studies were excluded from the review. Reasons for exclusion include: publication type (n=15), study design (n=44), population (n=18), intervention (n=53), comparator (n=21), outcomes (n=4), and duplicate (n=2). In addition, we were unable to obtain copies of 5 studies.

Publication type (n = 15)

1. IM Dihydroergotamine Comparable to Meperidine for Acute Migraine. Modern Medicine 1998;66(10):19.
2. Migraine treatments: Acute. headache: The Journal of Head & Face Pain 2005;45(4):401-2.
3. Bermejo PE, Pereda AF. Neuroleptics in the treatment of migraine. Med Clin (Barc) 2008;130(18):704-9.
4. 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.
5. 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.
6. Colman I, Innes GD, Brown MD, et al. Parenteral corticosteroids for acute migraine [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2011;(4).
7. Colman I, Innes GD, Brown MD, et al. Parenteral dihydroergotamine (DHE) for acute migraine [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2011;(4).
8. Colman I, Innes GD, Brown MD, et al. Parenteral metoclopramide for acute migraine [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2011;(4).
9. Dahlof C, Ekbom K, Persson L. Clinical experiences from Sweden on the use of subcutaneously administered sumatriptan in migraine and cluster headache. Arch Neurol 1994;51(12):1256-61.
10. Friedman BW. Treatment of primary headache in the emergency department. Headache: The Journal of Head & Face Pain 2004;44(7):728-30.
11. Hay E. Treatment of migraine with sumatriptan in the ED [8]. Am J Emerg Med 1994;12 (3):388-389.
12. Kostic M, Gutierrez F, Rieg T, Moore T, Gendron R. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. Headache 2010;50(5), 892.
13. Suthisisang CC, Poolsup N, Suksomboon N, et al. Meta-Analysis of the Efficacy and Safety of Naproxen Sodium in the Acute Treatment of Migraine. Headache: The Journal of Head & Face Pain 2010;50(5):808-18.
14. Tepper SJ. Migraine treatment. Headache: The Journal of Head & Face Pain 2005;45(3):264-5.
15. Vinson, DR. Emergency department treatment of migraine headaches. Arch Intern Med 2002;162(7):845.

Study design (n = 44)

1. Becker W, Riess C, Hoag J. Effectiveness of subcutaneous dihydroergotamine by home injection for migraine. Headache: The Journal of Head & Face Pain 1996;36(3):144-8.
2. Carpenter CR. Review: Adding dexamethasone to standard therapy reduces short-term relapse for acute migraine in the emergency department. Evidence Based Medicine 2009;14(4):121.
3. Carpenter CR. Review: Adding dexamethasone to standard therapy reduces short-term relapse for acute migraine in the emergency department : What kind of randomized trials do patients and clinicians need ? Ann Intern Med 2009;2009(10).
4. Centre for Reviews and Dissemination. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the emergency department: a meta-analysis and systematic review of the literature (Structured abstract). Database of Abstracts of Reviews of Effects 2011;(2) 2011;(2).
5. Centre for Reviews and Dissemination. Parenteral dexamethasone for acute severe migraine headache: meta-analysis of randomised controlled trials for preventing recurrence (Structured abstract). Database of Abstracts of Reviews of Effects 2011;(2) 2011;(2).
6. Centre for Reviews and Dissemination. The relative efficacy of phenothiazines for the treatment of acute migraine: a meta-analysis (Structured abstract). Database of Abstracts of Reviews of Effects 2011;(2) 2011;(2).
7. Centre for Reviews and Dissemination. The relative efficacy of meperidine for the treatment of acute migraine: a meta-analysis of randomized controlled

trials (Structured abstract). Database of Abstracts of Reviews of Effects 2011;(2) 2011;(2).
8. Colman I, Friedman 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.
9. Derry S, Moore AR. Diclofenac with or without an antiemetic for acute migraine headaches in adults [Protocol]. Cochrane Database of Systematic Reviews 2010;(10) 2011;(10).
10. Derry S, Moore AR, McQuay HJ. Eletriptan for acute migraine headaches in adults [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2010;(4).
11. Derry S, Moore AR, McQuay HJ. Naratriptan for acute migraine headaches in adults [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2010;(4).
12. Derry S, Moore AR, McQuay HJ. Paracetamol (acetaminophen) with or without an antiemetic for acute migraine headaches in adults [Systematic Review]. Cochrane Database of Systematic Reviews 2011;(1) 2010;(1).
13. Derry S, Moore AR, McQuay HJ. Zolmitriptan for acute migraine headaches in adults [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2010;(4).
14. Elstner M, Linn J, Muller-Schunk S, et al. Reversible cerebral vasoconstriction syndrome: A complicated clinical course treated with intra-arterial application of nimodipine. Cephalalgia 2009;29 (6):677-82.
15. Ferrari MD, Goadsby PJ, Roon KI, et al. Triptans (serotonin, 5-HT1B/1D agonists) in migraine: detailed results and methods of a meta-analysis of 53 trials. Cephalalgia 2002;22(8):633-58.
16. Freitag FG, Diamond S, Diamond M, et al. Subcutaneous sumatriptan in patients treated with monoamine oxidase inhibitors and other prophylactic agents. Headache Quarterly 1998;9 (2):165-71.
17. 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.
18. Friedman D, Feldon S, Holloway R, et al. Utilization, Diagnosis, Treatment and Cost of Migraine Treatment in the Emergency Department. Headache: The Journal of Head & Face Pain 2009;49(8):1163-73.
19. Fullerton T, Gengo FM. Sumatriptan - A Selective 5-Hydroxytryptamine Receptor Agonist for the Acute Treatment of Migraine. Ann Pharmacother 1992;26(6):800-8.
20. Gallagher RM. Emergency Treatment of Intractable Migraine. Headache: The Journal of Head & Face Pain 1985;25(3).
21. Gallagher RM. Emergency treatment of intractable migraine. Headache: The Journal of Head & Face Pain 1986;26(2):74-5.
22. Griffith JD, Mycyk MB, Kyriacou DN. Metoclopramide versus hydromorphone for the emergency department treatment of migraine headache. J P ain 2008;9(1):88-94.
23. Hernansanz MAC, Roy RS, Orgaz AC, et al. Migraine treatment patterns and patient satisfaction with prior therapy: a substudy of a multicenter trial of rizatriptan effectiveness. Clin Ther 2003;25(7):2053-69.
24. Kelly AM, Walcynski T, Gunn B. The Relative Efficacy of Phenothiazines for the Treatment of Acute Migraine: A Meta-Analysis. Headache: The Journal of Head & Face Pain 2009;49(9):1324-32.
25. Kirthi V, Derry S, Moore AR, et al. Aspirin with or without an antiemetic for acute migraine headaches in adults [Systematic Review]. Cochrane Database of Systematic Reviews 2010;(11) 2010;(11).
26. Lake AE, III, Saper JR, Hamel RL. Comprehensive inpatient treatment of refractory chronic daily headache. Headache: The Journal of Head & Face Pain 2009;49(4):555-62.
27. Law S, Derry S, Moore AR. Triptans for acute cluster headache [Systematic Review]. Cochrane Database of Systematic Reviews 2011;(1) 2010;(1).
28. Ling R, Derry S, Moore AR, et al. Rizatriptan for acute migraine headaches in adults [Protocol]. Cochrane Database of Systematic Reviews 2010;(4) 2010;(4).
29. Lipton RB, Bigal ME, Goadsby PJ. Double-blind clinical trials of oral triptans vs other classes of acute migraine medication - a review. Cephalalgia 2004;24(5):321-32.
30. Loder EW. Review: intravenous metoclopramide is better than placebo for reducing pain in acute migraine in the emergency department. ACP Journal Club 2004;142(3):77-Jun.
31. Lofland JH, Johnson NE, Batenhorst AS, et al. Changes in resource use and outcomes for patients with migraine treated with sumatriptan: A managed care perspective. Arch Intern Med 1999;159 (8):857-63.
32. McCrory DC, Gray RN. Oral sumatriptan for acute migraine [Systematic Review]. Cochrane Database of Systematic Reviews 2009;(1).
33. Oldman A, Smith LA, McQuay HJ, et al. Rizatriptan for acute migraine [Systematic Review]. Cochrane Database of Systematic Reviews 2011;(1) 2010;(1).
34. Richman PB, Reischel U, Ostrow A, et al. Droperidol for acute migraine headache. Am J Emerg Med 1999;17(4):398-400.
35. Sahai-Srivastava S, Desai P, Zheng L. Analysis of headache management in a busy emergency room in the United States. Headache: The Journal of Head & Face Pain 2008;48(6):931-8.
36. Silberstein SD, Schulman EA, McFadden HM. Repetitive intravenous DHE in the treatment of refractory headache. Headache 1990;30(6):334-39.
37. Singh A, Alter HJ, Zaia B. Does the addition of dexamethasone to standard therapy for acute migraine headache decrease the incidence of recurrent headache for patients treated in the

emergency department? A meta-analysis and systematic review of the literature. Acad Emerg Med 2008;15(12):1223-33.
38. Smith LA, Oldman A, McQuay HJ, et al. Eletriptan for acute migraine [Systematic Review]. Cochrane Database of Systematic Reviews 2011;(1) 2010;(1).
39. Takiya L, Piccininni LC, Kamath V. Safety and efficacy of eletriptan in the treatment of acute migraine. Pharmacotherapy 2006;26(1):115-28.
40. Tfelthansen P. Sumatriptan for the Treatment of Migraine Attacks - A Review of Controlled Clinical-Trials. Cephalalgia 1993;13(4):238-44.
41. Tornabene SV, Deutsch R, Davis DP, et al. Evaluating the Use and Timing of Opioids for the Treatment of Migraine Headaches in the Emergency Department. J Emerg Med 2009;36 (4):333-37.
42. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. Ann Emerg Med 2002;39(3):215-22.
43. 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.
44. Visser WH, de Vriend RH, Jaspers MW, et al. Sumatriptan in clinical practice: a 2-year review of 453 migraine patients. Neurology 1996;47(1):46-51.

Population (n = 18)

1. Aurora SK, Rozen TD, Kori SH, et al. A randomized, double blind, placebo-controlled study of MAP0004 in adult patients with migraine. Headache: The Journal of Head & Face Pain 2009;49(6):826-37.
2. Barrajon E, de las PR. Randomised double blind crossover study comparing ondansetron, granisetron and tropisetron. A cost-benefit analysis. Support Care Cancer 2000;8(4):323-33.
3. Bell CF, Foley KA, Barlas S, et al. Time to pain freedom and onset of pain relief with rizatriptan 10 mg and prescription usual-care oral medications in the acute treatment of migraine headaches: A multicenter, prospective, open-label, two-attack, crossover study. Clin Ther 2006;28(6):872-80.
4. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the acute treatment of episodic tension-type headache: a randomized, placebo controlled, double-blind study. Arq Neuropsiquiatr 2002;60(3-A):537-41.
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Appendix D. Risk of Bias Table

Reference list with complete citation appears at the end in alphabetical order.

Author Year	Sequence generation	Allocation concealment	Blinding: Subjective outcomes	Incomplete outcome data	Selective outcome reporting	Other sources	Overall risk of bias
Akpunonu 1995	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Aktas 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Low	Unclear
Alemdar 2007	Unclear	High	Unclear	Low	Low	Low	High
Baden 2006	Low	Low	Low	Low	Low	Low	Low
Belgrade 1989	Unclear	Unclear	High	Low	Low	Low	High
Bell 1990	Unclear	Unclear	Unclear	High	Low	Low	High
Bigal 2002	Low	Unclear	Unclear	Low	Unclear	Unclear	Unclear
Blanda 2001	Low	Low	Low	Low	Low	Low	Low
Cabarrocas 2001	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Cady 1991	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Callaham 1986	Unclear	Unclear	Low	Low	Low	Low	Unclear
Callan 2008	Low	Low	Low	Unclear	Low	Low	Unclear
Cameron 1995	Low	Low	Low	Low	Low	Low	Low
Carleton 1998	Low	Low	Low	Low	Low	Low	Low

Cete 2005	Low	Low	Low	Low	Low	Low	Low
Cicek 2004	Low	Unclear	Low	Low	Low	Low	Unclear
Coppola 1995	Low	Unclear	Unclear	Low	Low	Low	Unclear
Corbo 2001	Low	Low	Low	Low	Unclear	Low	Unclear
Davis 1995	Unclear	Low	Low	Low	Low	Low	Unclear
Demirkaya 2001	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Donaldson 2008	Unclear	Unclear	Low	Low	Low	Low	Unclear
Drotts 1999	High	Unclear	Unclear	Low	Low	Unclear	High
Duarte 1992	Unclear	Low	Low	Low	Low	Low	Unclear
Edwards 2001	Unclear	High	High	Low	Low	Low	High
Engindeniz 2005	Low	Low	Low	Low	Low	Low	Low
Fiesseler 2011	Low	Low	Low	Low	Low	Low	Low
Frank 2004	Low	Low	Low	Low	Low	Low	Low
Friedman 2006	Low	Low	Low	Low	Low	Low	Low
Friedman 2008	Low	Low	Low	Low	Low	Unclear	Unclear
Friedman 2005	Low	Low	Low	Low	Low	Unclear	Unclear
Friedman 2007	Low	Low	Low	Low	Low	Low	Low
Ginder 2000	Low	Low	Low	Low	Low	Low	Low
Hill 2008	Low	Low	Low	Unclear	Low	Low	Unclear

Hoag 1986	Low	Unclear	High	Low	Low	Unclear	High
Honkaniemi 2006	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Innes 1999	Unclear	Low	Low	Low	Low	Low	Low
Jones 2003	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Jones 1996	Low	Low	Low	Low	Low	Low	Low
Jones 1989	Low	Low	Low	Low	Low	Low	Low
Jovicic 1995	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Karachalios 1992	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Kelly 1997	Unclear	Unclear	High	Low	Low	Low	High
Klapper 1991	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Klapper 1991	Unclear	Unclear	Low	Low	Low	Unclear	Unclear
Kostic 2010	Low	Low	Low	Low	Low	Low	Low
Krymchantowski 2003	Unclear	Unclear	High	Low	Low	Low	High
Lane 1989	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Larkin 1992	Low	Unclear	Low	Low	Low	Low	Unclear
Limmroth 1999	High	Unclear	Unclear	Low	Low	Low	Unclear
McEwen 1987	Unclear	Low	Low	Low	Low	Low	Unclear
Meredith 2003	Low	Unclear	Low	Low	Low	Low	Unclear
Miller 2009	Low	Unclear	Low	Low	Low	Low	Unclear
Miner 2001	Low	Unclear	Low	Low	Unclear	Unclear	Unclear

Monzillo 2004	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear
Mushet 1996	Unclear	Unclear	Low	Low	Low	Low	Unclear
Richman 2002	Unclear	Unclear	Low	Low	Unclear	Unclear	Unclear
Rowe 2008	Low	Unclear	Low	Low	Low	Low	Unclear
Seim 1998	Low	Unclear	Low	Low	Low	Low	Unclear
Shrestha 1996	Low	Low	Low	Low	Low	Low	Low
Silberstein 2003	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Stiell 1991	Low	Low	Low	Low	Low	Low	Low
The Subcutaneous Sumatriptan International Study Group 1991	Low	Unclear	Unclear	Low	Low	Low	Unclear
Tanen 2003	Low	Low	Low	Low	Low	Low	Low
Teaheraghdam 2011	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Tek 1987	Low	Low	Low	Low	Low	Low	Low
Tek 1990	Low	Low	Low	Unclear	Low	Low	Unclear
Thomson 1993	Unclear	Unclear	Unclear	Low	Low	Low	Unclear
Vinson 2001	Low	Low	Low	Low	Low	Low	Low
Weaver 2004	Low	Low	Low	Low	Low	Unclear	Unclear
Wendt 2006	Unclear	Unclear	Low	Low	Unclear	Low	Unclear
Winner 1996	Unclear	Unclear	Unclear	Low	Low	Unclear	Unclear

Appendix E. Nonresponders Table

Author, year	Non-response definition	Nonresponse data		Not pain-free data		Relevance/Conclusions
		Treatment	Comparison	Treatment	Comparison	
Akpunonu, 1995	Failure of patient to achieve "meaningful relief" as defined by patient	SUM 22/88 = 25%	Placebo 31/48 = 65%	SUM 61/88 = 69%	Placebo 42/48 = 88%	NR
Aktas, 2011	Requirement of rescue medication (60 minutes after initial treatment)	OND 4/30 = 13.3%	MET 1/30 = 3%	NR	NR	NR
Alemdar, 2007	Failure to achieve decrease in VAS pain score by >50% of baseline value and a decrease of 4-point verbal scale score (60 minutes after initial treatment)	Tramadol 5/17 = 30%	Placebo 11/17 = 65%	Tramadol 12/17 = 71%	Placebo 15/17 = 88%	Headache recurrence within 24 hr of administration reported by 2 (16.7%) of 12 patients with pain response in the tramadol group, and 1 (16.7%) of 6 patients with pain response in the placebo group.
Baden, 2006	Failure to relieve all pain by ED discharge.	NR	NR	NR	NR	NR
Belgrade, 1989	Failure to achieve near-complete pain resolution (90% or greater)	MEP 22/22 = 100% BUT 16/19 = 84%	DHE 13/21 = 62%	NR	NR	NR
Bell, 1990	Patient requires addition medication (outside treatment protocol).	CPZ 5/24 = 21%	LID 11/26 = 42% DHE 13/26 = 50%	CPZ 16/24 = 67%	LID 24/26 = 92% DHE 6/26 = 77%	NR
Bigal, 2002	Failure to achieve pain reduction of <2 points on scale of 0 to 3 before discharge (60 minutes after initial treatment)	CPZ 12/68 = 18%	Placebo 51/60 = 85%	CPZ 24/68 = 35%	Placebo 55/60 = 92%	NR
Bigal, 2002		NR	NR	Diclofenac 28/30=93%	Placebo 19/30=63%	NR Foreign language

						(Portugese)
Blanda, 2001	< 50% improvement in pain score or an absolute pain score >2.5cm (VAS) 5 min after treatment	LID 25/27 = 93%	Placebo 19/22 = 86%	LID 9/27 = 33%	Placebo 6/22 = 27%	It may be that patients who had more severe pain were less likely to respond (at 5 min).
Cabarrocas, 2001	Failure to achieve a reduction in migraine pain from moderate or severe at baseline to mild or no pain (120 min after initial treatment)	Almotriptan 2mg: ~60% 6mg: 97% 10mg: 90%	Placebo 50%	Almotriptan 2mg: 74% 6mg: 41% 10mg: 61%	Placebo 75%	NR
Cady, 1991	Requirement of rescue medication	SUM 20%	Placebo 59%	SUM 223/734 = 30%	Placebo 290/370 = 78%	NR
Callaham, 1986	Requirement of rescue narcotics	DHE 0/19 = 0%	Placebo 4/15 = 27%	NR	NR	No factors correlated with treatment success.
Callan, 2008	Requirement of rescue medication 60 min after initial treatment (Failure to achieve improvement of 25mm on VAS scale)	PMZ 12/35 = 34%	PC 12/35 = 34%	NR	NR	*NR*
Cameron, 1995	Failure of patient to achieve >70% relief (Requirement of rescue medication)	CPZ 10/47 = 26%	MET 15/44 = 33%	CPZ 35/47 = 74%	MET 33/44 = 75%	NR
Carleton, 1998	Need for second treatment	DHE 30/85 = 39%	MEP 31/85 = 41%	NR	NR	NR
	Requirement of rescue medication	DHE 16/85 = 19%	MEP 14 /85 = 16%	NR	NR	NR
Cete, 2004	Requirement of rescue medication (30 min after initial treatment)	MEP 14/37=38% $MgSO_4$ 16/36 =44%	Placebo 26/40 = 65%	NR	NR	NR
Cicek, 2004	Required rescue medication (60 min after initial treatment)	MET 12/85 = 14% PET 35/84 = 42%	MET+PET 23/84 = 27% Placebo 52/83 =63%	NR	NR	NR
Coppola, 1995	Failure to achieve patient satisfaction and either a decrease of >50% in the	MET 52%	Placebo 71%	MET 6/24 = 25%	Placebo 15/24 = 63%	NR

	30-min pain score (compared with the initial score) or an absolute pain score of 2.5 cm or less.	PC 18%		PC 2/22 = 9%		
Corbo, 2001	Failure to obtain a 50% pain reduction (45 minutes after initial treatment)	MET+$MgSO_4$ 6/21 = 29%	MET+placebo 1/23 = 4%	NR	NR	NR
Davis, 1995	< 4 unit change in pain score (on 10-point Borg scale)	MEPT/PMZ 7/22 = 32%	Ketorolac 9/20 = 45%	NR	NR	Quotation: *if the patient's headache pain is reduced within 30 to 60 min, the patient can be given relatively good assurance that the migraine headache will continue to be suppressed for hours.*
Demirkaya, 2001	Failure to reduce headache pain from medium or severe to none or mild (30 min after initial treatment)	$MgSO_4$ 0/15 = 0%	Placebo 14/15 = 93%	$MgSO_4$ 2/15 =13.4%	Placebo 15/15 = 100%	NR
Donaldson, 2008	Failure to resolve headache in ED	NR	NR	DEX 30/57 = 53%	Placebo 27/42 = 64 %	NR
Drotts, 1999	NR	NR	NR	NR	NR	NR
Duarte, 1992	Patient fails to achieve "complete" or "great deal" of relief	KET 10/25 = 40%	MEP/HYD 11/25 = 44%	KET 24/25 = 96%	MEP/HYD 25/25 = 100%	NR
Edwards, 2001	Failure to achieve headache relief (from moderate to severe to mild or no headache) within 4 hr	VAL 40%	MET+DHE 40%	NR	NR	NR
Engindeniz, 2005	Failure to achieve headache relief (from pain score of 2 or 3 to 0 or 1) within 2 hr	Diclofenac sodium 4/20 = 20%	Tramadol 4/20 = 20%	Diclofenac sodium 11/20 = 55%	Tramadol 13/20 = 65%	NR
Fiesseler, 2011	Failure to resolve headache at 24 hr FU	DEX 15/46 = 33% Prednisone 18/48 = 38%	Placebo 36/82 = 44%	DEX (At D/C) 81/94 = 86%	Placebo (At D/C) 77/87 = 89%	NR
Frank, 2004a	<50% reduction in VAS pain score	$MgSO_4$ 17/21 = 81%	Placebo 16/21 = 76%	NR	NR	NR

Frank, 2004b	Patients requiring rescue therapy.	$MgSO_4$ 17/21 = 81%	Placebo 18/21 = 86%	NR	NR	NR
Friedman, 2005	Required rescue medication	MET/DPH 2/40 = 5%	SUM 10/38 = 26%	MET/DPH 16/40= 41%	SUM 24/38 = 65%	NR
Friedman, 2006	Failure to achieve mild or no headache pain at 2 hr post-treatment (required rescue medication)	TMB+DPH 4/20 = 20%	SUM 3/20 = 15%	TMB/DPH 14/20 = 70%	SUM 11/20 = 55%	NR
Friedman, 2007	Requirement of rescue medication	MET+DEX 14/106 = 13%	MET+Placebo 13/99 = 13%	MET+DEX 48/106 = 45%	MET+Placebo 52/99 = 53%	In the H/A > 72 hr subgroup, 38% of those receiving dexamethasone were persistently pain free vs 13% of placebo (p = 0.06).
Friedman, 2008	Required rescue medication (60 min after initial treatment)	PCZ 3/34 = 9%	MET 6/36 = 17%	PCZ 16/37 = 43%	MET 22/37 = 59%	Logistic regression analysis showed that duration of headache did not influence the 1-hr outcome (R2 = 0.00; P= 0.73).
Ginder, 2000	Partial (<45%) or no pain relief and requirement of additional pain medication	PCZ 10/20 = 50%	$MgSO_4$ 8/16 = 50%	PCZ 12/20 = 60%	$MgSO_4$ 14/16 = 88%	NR
Hill, 2008a	Failure to reduce pain from moderate or severe to mild or none (60 min after initial treatment)	Olanzapine 6/44 = 13.6%	DRO 5/40 = 12.5%	Olanzapine 28/45 =62%	DRO 31/45 =69%	NR
Hill, 2008b	Required rescue medication	Olanzapine 4/45 = 9%	DRO 6/42 =14%	(See above)	(see above)	NR
Hoag, 1986	Failure to achieve improvement above the median relief score of 2.2	MTP 30%	MEP+DHE 72%	NR	NR	NR
Honkaniemi, 2006	Failure to achieve “significant relief” within 3 hr of treatment	Haloperidol 4/20 = 20%	Placebo 17/20 = 85%	NR	NR	NR
Innes, 1999	Patients requiring > 1 abortive treatment.	DEX 25/49 = 51%	Placebo 26/49 = 53%	NR	NR	Post-hoc regression analysis showed an association between increased headache duration and severe recurrent headache, suggesting that the relative

						risk of recurrent severe headache increases by about 1%/hr of headache duration.
Jones, 1989	Any patient without relief (60 minutes after initial treatment)	PCZ 5/42 = 12%	Placebo 22/40 = 55%	PCZ 31/42 = 74%	Placebo 5/40 = 13%	Patients (treatment, and placebo) who achieved complete relief in the ED had no recurrence of headache within 48 hrs.
Jones, 1996	Required rescue analgesic (60 minutes after initial treatment)	PCZ 16/28 = 57% MET 23/29 = 79%	Placebo 25/29 = 86%	PCZ 19/28 = 68% MET 25/29 = 86%	Placebo 27/29 = 93%	
Jones, 2003		NR	NR			Abstract
Jovicic, 1995		NR	NR	NR	NR	Foreign language
Karachallios, 1992	Failure to achieve complete pain relief	Diclofenac sodium 5/45 = 12%	Paracetamol 33/40 = 82.5%	Diclofenac sodium Same result	NR	NR
Kelly, 1997	Failure to relieve pain to patient satisfaction	SUM 1/20 = 5%	CPZ 1/23 = 4%	SUM 58%	CPZ 59%	NR
Klapper, 1986	Pain improvement of <1 pain unit, and patient felt unable to return to normal functioning	DEX+MET 5/11 = 46% DHE+MET 4/9 = 44%	Placebo 0/10 = 0%	NR	NR	NR
Klapper, 1991	Moderate pain and requirement of rescue medication (60 min after initial treatment)	KET 6/9 = 67%	DHE+MET 0/8 = 0%			NR
Kostic, 2010		NR	NR	NR	NR	NR
Krymchantowski, 2003	Requirement of rescue medication (120 min after initial treatment)	LC 1/17 = 6%	Placebo 6/12 = 50%	LC 3/17 = 18%	Placebo 7/12 = 58%	NR
Lane, 1989	Requirement of rescue medication after 3 treatments (45 min after initial treatment)	CPZ 2/24 = 8%	MEP+DHE 11/22 = 50%	NR	NR	NR

Larkin, 1992	Requirement of rescue medication	KET 11/15 = 73%	MEP 6/16 = 36%	KET 14/15 = 95% (Figure 2)	MEP 11/16 = 70% (Figure 2)	NR
Limroth, 1999	Pain relief of less than 50% (60 min after initial treatment)	L-ASA 31/56 = 55%	Ergot 43/56 = 77%	NR	NR	NR
McEwen, 1987	Requirement of rescue medication	CPZ 8/19 = 42%	Placebo 14/17 = 82%	CPZ 18/19 = 95%	Placebo 17/17 = 100%	NR
Meredith, 2003	Requirement of rescue medication at end of study period	SUM 4/16 = 25%	KET 2/13 = 15%	NR	NR	NR
Miller, 2009	Failure to achieve patient satisfaction with treatment and either a decrease of 50% or more in the pain score when compared with the initial score or an absolute pain score of 2.5 cm or less (Required rescue medication)	PCZ 2/20 = 10%	OC 11/23 = 48%	NR	NR	NR
Miner, 2001	Failure to obtain least a 50% reduction from their baseline VAS scores (60 min after initial treatment)	DRO 8/82 = 98%	PCZ 27/86 = 31%	NR	NR	NR
Monzillo, 2004		NR	NR	Haloperidol 0/14=0%	DEX 13/15 = 53.4%	NR Foreign language
Mushet, 1996	Pain reduction of <2 points on scale of 0 to 3 (60 min after initial treatment)	SUM Study 1: 30% Study 2: 23%	Placebo Study 1: 75% Study 2: 68%	SUM -120 mins Study 1: ~40% Study 2: ~44% (Figure)	Placebo -120 mins Study 1: ~91% Study 2: ~90% (Figure)	NR
Richman, 2002	Patient not well enough to go home after 30 min and thus requiring rescue medication	DRO 33%	MEP 43%	NR	NR	NR
Rowe, 2007	score of > 2 on the VAS scale at the end of treatment (which varied)	DEX 24/64 = 38%	Placebo 23/62 = 37%	NR	NR	VAS >2 at end of treatment had more relapse than responders (~38% vs ~20%)
Seim, 1998	Requirement of rescue treatment (60 min after initial treatment)	PCZ 6/35 = 17%	KET 4/29 = 14%	NR	NR	NR

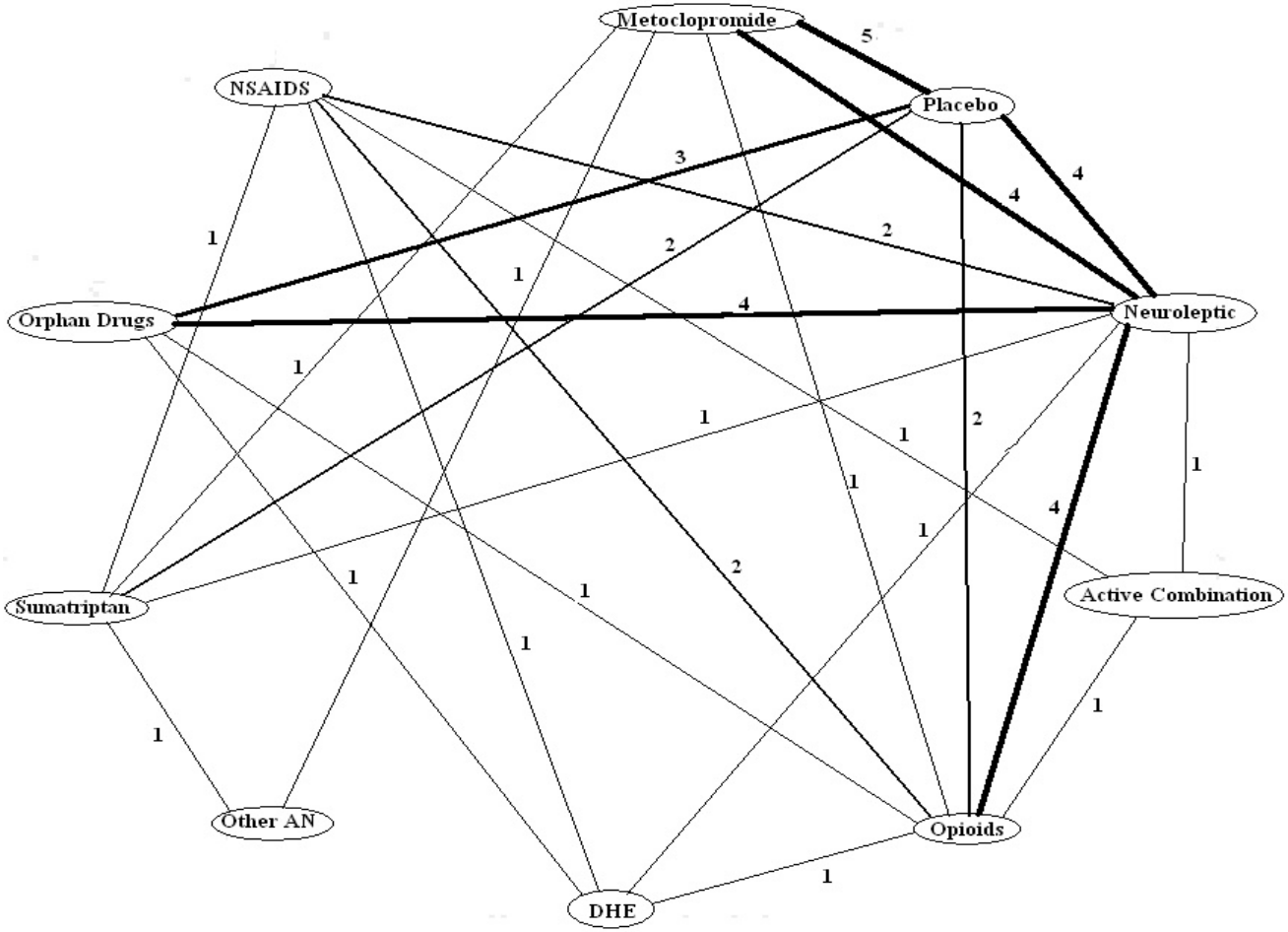
Shresta, 1997	Requirement of rescue medication (120 min after initial treatment)	KET 1/15 = 7%	CPZ 2/15 = 13%	KET 6/15 = 40%	CPZ 6/15 = 40%	NR
Stiell, 1991	Failure of patient to achieve >70% relief, requiring rescue medication	MEP/DHE 27.0%	MTZ 29.7%	NR	NR	NR
Tanen, 2003	Requirement of rescue medication (60 min after initial treatment)	VAL 15/19 = 79%	PCZ 5/20 = 25%	NR	NR	NR
Tek, 1990	"No relief of pain"	MET 8/24 = 33%	Placebo 21/26 = 81%	NR	NR	NR
Tek, 1987	Requirement of rescue medication	NR	NR	NR	NR	NR
Thomson, 1993a	Failure to achieve significant improvement in pain (i.e. grade 2 or 3 to grade 0 or 1) within 30 min	SUM 10/28 = 36%	Placebo 16/22 = 73%	SUM 23/28 = 82% (30 minutes)	Placebo 21/22 = 95% (30 minutes)	NR
Thomson, 1993b	Patients requiring rescue therapy	SUM 9/28 = 32%	Placebo 17/22 = 75%	(See above)	(See above)	NR
Vinson, 2001		NR	NR	NR	NR	NR
Weaver, 2004	Failure to achieve 50% pain relief (30 min after initial treatment)	DRO 8/48 = 17%	PCZ 34/47 = 28%	DRO 22/48 = 46%	PCZ 29/47 = 62%	NR
Wendt, 2006	Failure to reduce moderate or severe pain to mild or no pain (120 min after initial treatment)	SUM 30%	Placebo 78%	SUM 50%	Placebo 89%	NR
Winner, 1996a	Failure to achieve relief by 3 hr (i.e. required rescue mediation)	DHE 20/145 = 14%	SUM 15/150 = 10%	DHE 27/145 = 19%	SUM 46/150 = 30%	NR
Winner, 1996b	Patients requiring rescue therapy	DHE 43/145 = 30%	SUM 23/150 = 15%	(See above)	(See above)	NR

BUT: Butorphanol; CPZ: chlorpromazine; DHE: Dihydroergotamine; DEX: Dexamethasone; DPH Diphenhydramine; DRO: Droperidol; DiNa: diclofenac sodium; Ergot: Ergotamine; HDZ: Hydroxyzine; KET: Ketorolac; L-ASA: Lysine-Acetylsalicylic Acid; LC: Lysine Clonixinate; LID: Lidocaine; MEP: Meperidine; MgSO4: Magnesium sulphate; MTP: Metroclopamide; MTZ: Methotrimeprazine; NR = not reported; OC: Octreotide; OND: Ondansetron; PCZ: Prochlorperazine; PMZ: Promethazine; SUM: Sumatripan; TMB: Trimethobenzamide; VAL: Valporate.

Appendix F. Network Diagrams for the Mixed Treatment Analyses

F.1. Pain (Visual analog scale)

This figure illustrates the comparisons and number of randomized controlled trials for each that were examined in the network meta-analysis for pain (VAS).



AN = anti-nauseants; DHE = dihydroergotamine; NSAIDS = nonsteroidal anti-inflammatory drugs

F.2. Akathisia

This figure illustrates the comparisons and number of randomized controlled trials for each that were examined in the network meta-analysis for akathesia.