Headache
© 2016 American Headache Society
ISSN 0017-8748
doi: 10.1111/head.12835
Published by Wiley Periodicals, Inc.

Review Article

Management of Adults With Acute Migraine in the Emergency Department: The American Headache Society Evidence Assessment of Parenteral Pharmacotherapies

Serena L. Orr, MD; Benjamin W. Friedman, MD, MS; Suzanne Christie, MD, FRCPC; Mia T. Minen, MD; Cynthia Bamford, MD; Nancy E. Kelley, MD, PhD; Deborah Tepper, MD

Objective.—To provide evidence-based treatment recommendations for adults with acute migraine who require treatment with injectable medication in an emergency department (ED). We addressed two clinically relevant questions: (1) Which injectable medications should be considered first-line treatment for adults who present to an ED with acute migraine? (2) Do parenteral corticosteroids prevent recurrence of migraine in adults discharged from an ED?

Methods.—The American Headache Society convened an expert panel of authors who defined a search strategy and then performed a search of Medline, Embase, the Cochrane database and clinical trial registries from inception through 2015. Identified articles were rated using the American Academy of Neurology's risk of bias tool. For each medication, the expert panel determined likelihood of efficacy. Recommendations were created accounting for efficacy, adverse events, availability of alternate therapies, and principles of medication action.

Results/Conclusions.—The search identified 68 unique randomized controlled trials utilizing 28 injectable medications. Of these, 19 were rated class 1 (low risk of bias), 21 were rated class 2 (higher risk of bias), and 28 were rated class 3 (highest risk of bias). Metoclopramide, prochlorperazine, and sumatriptan each had multiple class 1 studies supporting acute efficacy, as did dexamethasone for prevention of headache recurrence. All other medications had lower levels of evidence.

Recommendations.—Intravenous metoclopramide and prochlorperazine, and subcutaneous sumatriptan should be offered to eligible adults who present to an ED with acute migraine (Should offer—Level B). Dexamethasone should be offered to these patients to prevent recurrence of headache (Should offer—Level B). Because of lack of evidence demonstrating efficacy and concern about sub-acute or long-term sequelae, injectable morphine and hydromorphone are best avoided as first-line therapy (May avoid–Level C).

Key words: acute migraine, emergency department, adults, parenteral pharmacotherapies

(*Headache* 2016;56:911-940)

From the University of Ottawa, Ottawa, Ontario, Canada (S.L. Orr and S. Christie); Albert Einstein College of Medicine, Bronx, NY, USA (B.W. Friedman); New York University Langone Medical Center, New York, NY, USA (M.T. Minen); Cleveland Clinic, Cleveland, OH, USA (C. Bamford); Geisinger Medical Center, Danville, PA, USA (N.E. Kelley); Beth Israel Deaconess, Sandwich, MA, USA (D. Tepper)

Address all correspondence to B.W. Friedman, Department of Emergency Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, 111 East 210th Street, Bronx, NY 10467, USA. Email: bwfriedmanmd@gmail.com

Accepted for publication April 13, 2016.

INTRODUCTION

Background and Justification.—Acute migraine causes 1.2 million visits to US emergency departments (ED) annually.[1] More than 20 different parenteral medications and combinations of medications are used to treat migraine in US EDs, including migraine-specific medications such as sumatriptan and dihydroergotamine (DHE), anti-dopaminergics, such as metoclopramide and the neuroleptic

Conflict of Interest: The authors have no financial conflicts of interest to report.

prochlorperazine, opioids, corticosteroids, nonsteroidal anti-inflammatory drugs, and anti-histamines such as diphenhydramine and promethazine.[1,2] The causes of this heterogeneity in emergency practice have not been explored systematically but are probably multifactorial and include physician comfort and familiarity with specific medications, concern about short-term side effects, beliefs about efficacy, and response to patient request. The ideal parenteral medication would offer rapid and sustained headache freedom, without short or long-term sequelae, and allow patients to return rapidly to work or usual daily activities. Unfortunately, such a medication does not exist. Published clinical trials demonstrate that fewer than 25% of patients experienced sustained headache freedom after treatment of acute migraine in the ED.[3] Many of the medication classes listed above have been associated with irreversible but uncommon side effects such as ischemic vascular complications with migraine-specific medications, tardive dyskinesia with anti-dopaminergics, avascular osteonecrosis with corticosteroids, gastrointestinal hemorrhage with NSAIDs, and medication dependence with opioids. ED-based clinical trials have only rarely followed patients for a sufficiently long period of time. Few of these studies had adequate power to detect these uncommon downstream sequelae. Given the very large number of migraineurs presenting to US EDs annually, the heterogeneity in current emergency practice, and the frequent use of potentially harmful medications, it is important to know which parenteral medications should be considered first-line therapy.

Clinical Question Statement.—The purpose of this guideline is to provide an evidence-based answer to each of the following questions.

1. Which injectable medications should be considered first-line treatment for adults who present to an ED with acute migraine?
2. Do parenteral corticosteroids prevent recurrence of migraine in adults discharged from an ED?

METHODS

Authorship Committee.—The American Headache Society (AHS) Guideline Committee determined the need for a guideline statement on this topic and assembled a panel of AHS members with the expertise required to develop this guideline. As per AHS's policy, the authorship committee adhered to the American Academy of Neurology's Clinical Practice Guideline Process Manual[4] with regard to searching, abstracting, synthesizing, and grading the quality of the evidence, as well as using the available evidence to construct a guideline statement. The AHS provided a meeting room for the participants during its 57th annual national meeting in Washington, DC (June 18th, 2015). No other material support was provided. No outside funding was used throughout this guideline development. The AHS's guidelines committee and executive board approved this statement.

Search Strategy.—In consultation with a medical research librarian, we developed a comprehensive search strategy to ensure that all relevant evidence was considered. For the first question, we aimed to identify all randomized studies of adults with acute migraine in which an injectable therapeutic was compared to placebo or to an active control. Studies were included only if the headache met International Classification of Headache Disorder migraine criteria.[5] Acceptable routes of drug delivery included intravenous, intramuscular, and subcutaneous injections. To qualify for inclusion, the study needed to measure acute outcomes, defined as assessment within 6 hours of medication administration. For the second question, we aimed to identify all randomized studies of adults with acute migraine in which a corticosteroid medication was compared to placebo. Again, studies were included only if the headache met International Classification of Headache Disorder migraine criteria.[5] To qualify for inclusion, the study needed to measure subacute outcomes, defined as an assessment within 1 week of ED discharge. For both questions, we searched for published studies in the Medline, Embase, and Cochrane Central Register of Controlled Trials databases and looked for additional unpublished studies using two registries: http://clinicaltrials.gov and the WHO International Clinical Trial Registry Platform. In addition, we searched references of included studies. Our search strategy is presented in more detail in Figure S1.

Study Selection.—We used a two-step process to select studies. Two authors (S.L.O., S.C.) reviewed all abstracts identified in the search. Many of these abstracts were rejected out of hand as not relevant. At least two authors (S.L.O., B.W.F., S.C.) performed a more detailed review of studies deemed potentially eligible. Disagreements about whether or not the study met selection criteria were resolved through discussions among three members (S.L.O., B.W.F., S.C.) of the panel.

Data Abstraction.—Data abstraction was performed by one author and verified by a second (S.L.O., B.W.F., S.C.). We developed a Characteristics of Study worksheet, which was used for each included study. On this worksheet, we recorded information about the study characteristics, setting, participants, interventions, and outcomes.

Classifying the Evidence–Risk of Bias.—We used the American Academy of Neurology's risk of bias tool to grade study quality (Appendix 1).[4] With this instrument, randomized studies receive the highest score if they provided a clear description of eligibility criteria, assessed outcomes in a masked and objective manner, concealed allocation, used no more than two primary outcomes, accounted for discrepancies in baseline characteristics, and if at least 80% of randomized patients were available for data analysis. Crossover studies were required additionally to have a sufficient washout period, no period effect, and to have used appropriate statistics. Using this instrument, the highest quality RCTs received a class 1 grade, and the lowest quality RCTs received a class 3 grade. Nonrandomized studies were not considered as primary evidence in this review. At least two authors (S.L.O., B.W.F., S.C.) graded each study. Discrepancies were resolved through discussion and, if needed, a third panel member was consulted to break the tie.

Synthesizing the Evidence (Formulating Evidence-Based Conclusions).—For each acute migraine therapeutic, we considered the quality of the available evidence and the magnitude, precision, and consistency of results. Studies conducted in an ED were prioritized over studies conducted in the clinic or outpatient setting. Meta-analysis was performed when there were both a sufficient number of homogeneous studies and uncertainty with regard to the direction, magnitude, or precision of results. Sufficient homogeneity required at least two studies to have used the same medication, the same comparator, and the same outcome. The Cochrane Collaborations' Review Manager 5.3.5 software (RevMan: http://tech.cochrane.org/revman) was used to perform the meta-analysis. An assessment of statistical heterogeneity was performed using the chi square test, in which the threshold for considering a body of evidence heterogeneous was set at $P \leq .1$, and the I-squared test, where the threshold was set at $\geq 30\%$. This result, combined with an assessment of clinical heterogeneity, was used to determine whether to use a fixed or random effects model. Event rates and sample sizes were entered into the RevMan software and the appropriate Mantel-Haenszel model (fixed or random effects) was selected to compute odds ratios and 95% confidence intervals.

For each medication, we came to a conclusion about certainty of efficacy. Multiple class 1 studies with a consistent conclusion led to a *highly likely* to be effective (or ineffective) conclusion. One class 1 study or multiple class 2 studies resulted in a *likely* to be effective (or ineffective) conclusion. Multiple class 3 or one class 2 study resulted in a *possibly* effective (or ineffective) conclusion. Lower levels of evidence or conflicting evidence resulted in the following conclusion: there is insufficient evidence to support or refute efficacy.

Developing Recommendations.—We attempted to create a recommendation for every medication included in the studies identified in our search. We also attempted to create a recommendation for every medication used in more than 5% of US ED migraine visits. To determine whether a medication was used in more than 5% of US ED migraine visits, we relied on the National Hospital Ambulatory Medical Care survey, a publically available probabilistic sample published by the National Center for Health Statistics.[6] Recommendations were based largely on conclusions about the certainty of efficacy (Appendix 2). We weighed certainty of efficacy against frequency and severity of adverse medication effects. Absent clear evidence of

efficacy (or lack of efficacy), we considered inferences from widely accepted principles about medication effects on pain or the central nervous system. We contextualized rare, but potentially life-altering, adverse medication effects using published literature.

RESULTS

Our search identified 2050 studies of which 68 were included in the review (PRISMA flow diagram, Fig. 1). These 68 studies included 28 different injectable medications. Of the 68 studies, 19 were rated class 1 (low risk of bias), 21 were rated class 2 (higher risk of bias), and 28 were rated class 3 (highest risk of bias). Our search for question #2 did not reveal any eligible studies that did not appear in the search for question #1 because all eligible corticosteroid RCTs utilized injectable medication.

Which Injectable Medications Should Be Considered First-Line Treatment for Adults Who Present to an ED With Acute Migraine?—*Acetaminophen.*—We identified three studies of IV acetaminophen (Table S1).[7–9] In one class 1 study, in which 60 patients were randomized to acetaminophen 1000 mg or placebo, a comparable number of patients were pain free at 2 hours.[8] In the acetaminophen arm, 4/30 (13%) patients had minor adverse events.

In a class 2 study, in which 200 patients were randomized to acetaminophen 1000 mg or dexketoprofen 50 mg, pain scores were comparable 15 and 30 minutes after medication administration.[9] There were no adverse events in either group.

In a class 3 study of 148 patients, propacetamol 1000 mg, a prodrug of acetaminophen, outperformed rizatriptan 5 mg PO at 60 minutes, though not at 30 or 120 minutes.[7] In this study, adverse events were not reported.

Acetylsalicylic Acid.—We identified four randomized studies of intravenous acetylsalicylic acid.[10–13] A class 2 study randomized 275 adults to 1 gm acetylsalicylic acid, sumatriptan 6 mg SC or placebo.[10] Sumatriptan and acetylsalicylic acid both outperformed placebo. Sumatriptan also outperformed acetylsalicylic acid. However, the latter was tolerated as well as placebo, with significantly fewer adverse events than sumatriptan.

A class 2 study randomized 40 adults to 1 gm of lysine acetylsalicylic acid or 800 mg of valproic acid.[11] Pain relief at 1 hour and sustained pain freedom for 24 hours were comparable between the groups. No adverse events were reported in either arm.

Another class 2 study randomized 40 patients to 500 mg of acetylsalicylic acid or placebo.[13] The active arm demonstrated greater pain relief on a visual analog scale (VAS). No adverse events were reported in either group.

In a class 3 study, 56 patients were randomized to 1 gm acetylsalicylic acid or 0.5 mg ergotamine SC.[12] Substantially more patients in the acetylsalicylic arm achieved the primary outcome. These acetylsalicylic acid patients also tolerated the medication better than those given ergotamine.

Chlorpromazine.—We identified three randomized studies of parenteral chlorpromazine.[14–16] A class 2 study randomized 60 adults to chlorpromazine 0.1 mg/kg or placebo.[14] The chlorpromazine group reported greater improvements in pain at 30 and 60 minutes than placebo, though patients in the active group reported more adverse events, most commonly orthostatic hypotension and drowsiness.

In a class 3 study, 91 patients were randomized to chlorpromazine 0.1 mg/kg or metoclopramide 0.1 mg/kg.[15] Efficacy and adverse events were comparable between the groups.

In another class 3 study, 30 patients were randomized to chlorpromazine 25 mg IV or ketorolac 60 mg IM.[16] At 2 hours, there was no difference between the groups in pain outcomes. No adverse events were reported in either group.

Dexamethasone.—We identified four randomized studies in which dexamethasone was compared to an active comparator or placebo and acute outcomes were ascertained.[17–20] In a class 1 study, 205 patients were treated with metoclopramide and diphenhydramine.[18] Patients were then randomized to dexamethasone 10 mg IV or placebo. There was no difference between the groups in the proportion of patients achieving pain freedom at 2 hours or in the frequency of adverse events, though more patients in the dexamethasone arm developed localized pain reactions.

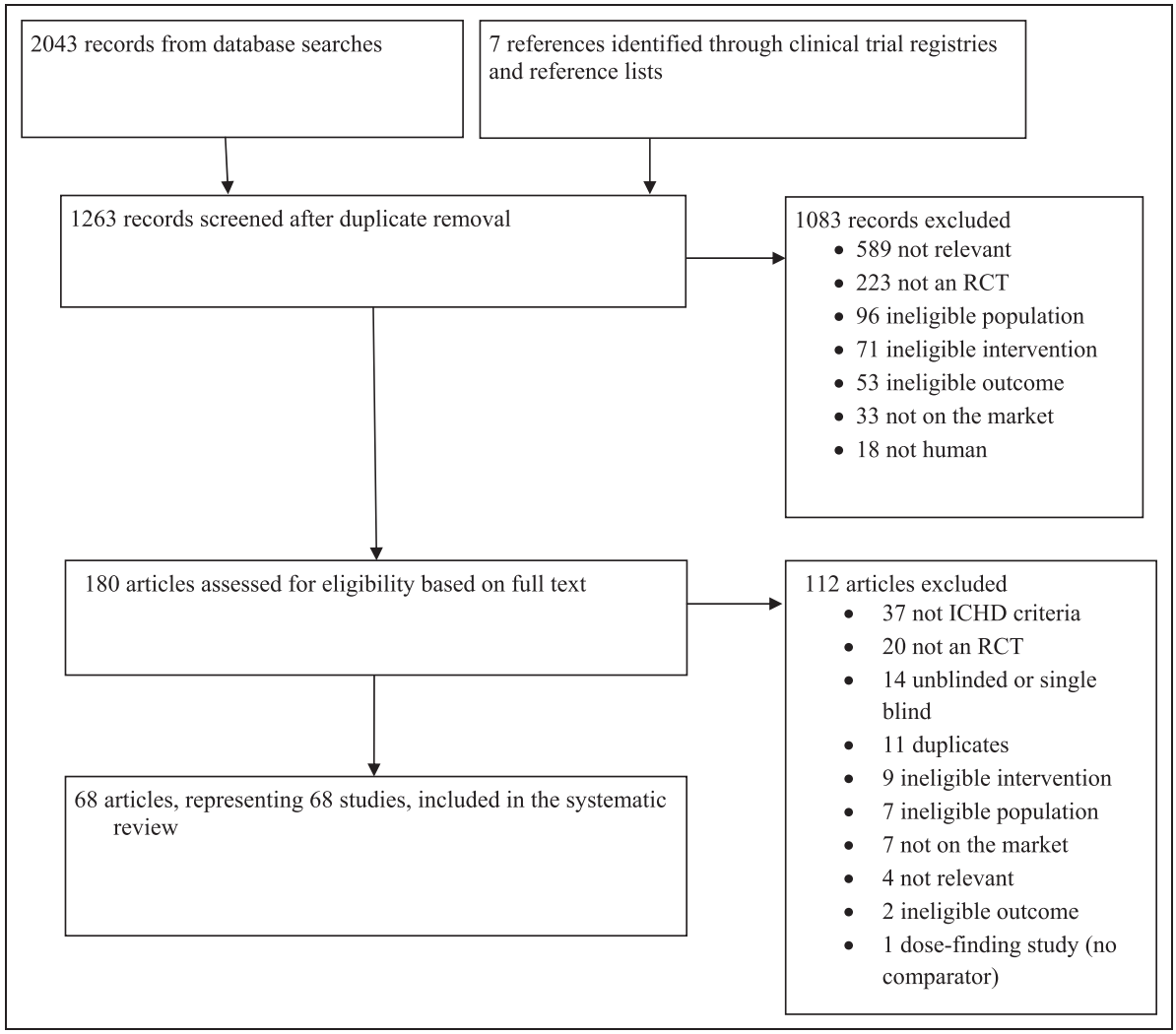

Fig. 1.—PRISMA diagram.

In a class 2 study, 190 patients were randomized to dexamethasone 8 mg IV or morphine 0.1 mg/kg IV.[20] Patients randomized to morphine reported lower pain scores at 1 hour, though the between-group difference was less than standard thresholds for clinical significance.[21] Adverse events were not reported in this study.

In a class 3 study, 31 patients were randomized to dexamethasone 16 mg IV or valproic acid 900 mg IV.[17] In this study, there were no differences between the groups in improvement in pain score. No adverse events were reported in this study.

In another class 3 study, 90 patients were randomized to dexamethasone 0.15 mg/kg IV or propofol 10 mg IV, dosed every 5–10 minutes up to 80 mg.[19] Patients in the propofol group reported greater decreases in pain intensity at all time points up to 45 minutes. Patients in the propofol group were very likely to report sedation. Oxygen desaturations occurred in two patients who received propofol.

Dexketoprofen.—We identified two randomized studies of dexketoprofen.[9,22] In a class 1 study, 224 adults were randomized to dexketoprofen 50 mg IV or placebo.[22] The active group had substantially greater improvement in pain intensity at 30 and 45 minutes. No adverse events were reported.

In a class 2 study, 200 adults were randomized to dexketoprofen 50 mg or acetaminophen 1 gm.[9]

Fifteen and 30 minutes after medication administration, there were no differences in pain scores. No adverse events were reported in either group.

Diclofenac.—We identified three randomized studies of diclofenac.[23–25] A class 3 study randomized 120 patients to diclofenac 75 mg IM or placebo.[23] At 1 hour, the diclofenac patients had greater rates of headache relief than placebo. Adverse events were not reported.

Another class 3 study randomized 47 patients to diclofenac 75 mg IM or tramadol 100 mg IM.[24] There were no between-group differences in any outcomes. Adverse events were uncommon.

A third class 3 study randomized 34 adults to diclofenac 75 mg IM or DHE 1 mg IM.[25] All patients received metoclopramide 10 mg IV. Outcomes at 1 and 2 hours were mixed. Adverse events were not reported.

Dihydroergotamine.—We identified two randomized studies of DHE.[25,26] In a class 3 study, 310 patients were randomized to DHE 1 mg SC or sumatriptan 6 mg SC. Outcomes favored sumatriptan at 1 and 2 hours though not at 3 hours. There were 305 adverse events reported among the 152 patients who received DHE and 238 adverse events among the 158 patients who received sumatriptan.

In another class 3 study, 34 adults were randomized to DHE 1 mg IM or diclofenac 75 mg IM. All patients received metoclopramide 10 mg IV. Outcomes at 1 and 2 hours were mixed. Adverse events were not reported.

Diphenhydramine.—We identified one study of diphenhydramine for migraine.[27] In a class 1 study, there were no differences in outcomes or adverse events among 208 adults randomized to diphenhydramine 50 mg IV or placebo. All patients received metoclopramide 10 mg IV. A discussion of the efficacy of diphenhydramine to prevent extrapyramidal symptoms is beyond the scope of this review. However, in this class 1 study, in which all patients were administered IV metoclopramide, there was no difference in the rate of extrapyramidal symptoms between those who received diphenhydramine and those who did not.

Dipyrone.—We identified two randomized studies of dipyrone for migraine.[28,29] In a class 2 study, 134 adults were randomized to intravenous dipyrone 1 gm or placebo.[29] The active arm had greater headache relief at 30 and 60 minutes. There was no difference in the overall rate of adverse events.

In another class 2 study, 27 adults were randomized to dipyrone or metoclopramide.[28] There was no difference in pain intensity at 2 hours. No significant adverse events were reported.

Droperidol.—We identified two randomized studies of droperidol.[30,31] In a class 2 study, 305 patients were randomized to placebo or to doses of IM droperidol ranging from 0.1 to 8.25 mg.[30] Doses of droperidol from 2.75 to 8.25 mg outperformed placebo with regard to headache response at 2 hours. Adverse events were greater among those who received the active medication.

In a class 3 study, 29 adults were randomized to droperidol 2.5 mg IM or meperidine 1.5 mg/kg IM.[31] There were no between group differences in efficacy. Akathisia occurred in 13% of those who received droperidol. Sedation occurred in 7% of the droperidol arm.

Ergotamine.—We identified one class 3 study of ergotamine, in which ergotamine 0.5 mg SC was compared with 1 gm of IV acetylsalicylic acid.[12] More patients in the acetylsalicylic acid group achieved a 50% pain reduction while more patients in the ergotamine group reported nausea and vomiting.

Haloperidol.—We identified two randomized studies of haloperidol.[32,33] In a class 1 study, 64 patients were randomized to haloperidol 5 mg IV or metoclopramide 10 mg IV.[32] All patients also received diphenhydramine 25 mg IV. There were no statistically significant differences in change in pain intensity, the primary outcome, though use of rescue medication was less common in the haloperidol group. Side effects were comparable between the two arms.

In a class 3 study, 40 adults were randomized to haloperidol 5 mg IV or placebo.[33] Substantially more participants in the haloperidol group reported marked relief, though 80% of the haloperidol group

reported side effects including 53% with motor agitation.

Ketamine.—We identified one class 3 crossover study of ketamine in which 17 adults were randomized to ketamine 0.08 mg/kg or placebo.[34] Patients who received ketamine reported significantly larger decreases in pain intensity, though feelings of fatigue or insobriety were common.

Ketorolac.—We identified four randomized studies of ketorolac.[16,35–37] In a class 1 study, 330 patients were randomized to ketorolac 30 mg IV, metoclopramide 10 mg IV, or valproate 1 gm IV.[36] Ketorolac and metoclopramide demonstrated similar rates of headache relief at 1 and 48 hour sustained relief, and both were superior to valproic acid. Overall adverse event rates were comparable.

In a class 3 study, 47 patients during 50 ED visits were randomized to ketorolac 60 mg IM or meperidine 100 mg + hydroxyzine 50 mg IM.[35] There were no significant differences between the groups with regard to efficacy or adverse events.

A second class 3 study randomized 31 patients to ketorolac 30 mg IM or meperidine 75 mg IM.[37] The ketorolac group experienced significantly less pain reduction at 1 hour than the meperidine group. Adverse events were comparable.

In a third class 3 study, 30 patients were randomized to ketorolac 60 mg IM or chlorpromazine 25 mg IV.[16] Results at 2 hours were comparable. Adverse events were not reported.

Lidocaine.—In a class 2 study, 25 patients were randomized to lidocaine 1 mg/kg or normal saline.[38] There were no differences in efficacy between groups. No adverse events were reported.

Lysine Clonixinate.—In a class 3 study, 29 patients were randomized to IV lysine clonixinate or placebo.[39] Lysine clonixinate had higher rates of headache freedom at 60 and 90 minutes, though adverse events were more common in this group as well.

Magnesium.—We identified five randomized studies of magnesium.[40–44] In a class 1 study, 44 patients were randomized to magnesium 2 gm IV or placebo.[42] All patients also received metoclopramide 20 mg IV. There was no statistically significant difference in the primary outcome, which was improvement on a VAS between baseline and ED discharge, though more patients randomized to placebo improved by $\geq$50% on the VAS and more placebo patients reported normal functionality at the time of ED discharge. Adverse events were more common in the magnesium arm.

In a class 2 study, 70 patients were randomized to magnesium 1 gm IV or dexamethasone 8 mg + metoclopramide 10 mg IV.[44] Patients randomized to magnesium reported greater decreases in pain intensity at 20 minutes, 1 hour, and 2 hours as compared to dexamethasone + metoclopramide. There was no difference in the frequency of adverse events.

In another class 2 study, 60 patients were randomized to magnesium 1 gm or placebo.[40] Magnesium demonstrated greater headache relief and headache freedom at 30 and 60 minutes among those patients with migraine with aura, though not among those without aura. Adverse events were not reported.

In a class 3 study, 30 patients were randomized to magnesium 2 gm IV or placebo.[43] Nearly every magnesium patient reported improvement vs none in the placebo group. Flushing was more common among those who received magnesium.

In another class 3 study, 113 patients were randomized to magnesium 2 gm IV, metoclopramide 10 mg IV, or placebo.[41] There were no statistically significant differences between groups with regard to pain intensity at 30 minutes. Flushing was more common in the magnesium group.

Meperidine.—We identified three randomized studies of meperidine.[31,35,37] In a class 3 study, 47 patients (during 50 visits) were randomized to meperidine 100 mg + hydroxyzine 50 mg IM or ketorolac 60 mg IM.[35] There were no significant differences between groups in the frequency of headache relief or side effects.

In another class 3 study, 31 adults were randomized to meperidine 75 mg IM or ketorolac 30 mg IM.[37] Those randomized to meperidine reported greater pain relief. Adverse events were comparable.

In a class 3 study, 29 patients were randomized to meperidine 1.5 mg/kg IM or droperidol 2.5 mg IM.[31] Efficacy results were comparable as was drowsiness.

Metoclopramide.—We identified 8 randomized studies of metoclopramide.[15,28,32,36,41,45–47] In a class 1 study, 64 patients were randomized to metoclopramide 10 mg IV or haloperidol 5 mg IV.[32] All patients were also treated with diphenhydramine 25 mg IV. There was no statistically significant difference in pain relief at 80 minutes. Patients in the haloperidol arm required rescue medication less frequently. The frequency of adverse events was comparable.

In another class 1 study, 330 patients were randomized to metoclopramide 10 mg IV, ketorolac 30 mg IV, or valproate 1 gm IV.[36] Metoclopramide and ketorolac demonstrated similar rates of headache relief at 1 and 48 hour sustained relief, and both were superior to valproic acid. Overall adverse event rates were comparable.

In a third class 1 study, 77 adults were randomized to metoclopramide 20 mg IV or prochlorperazine 10 mg IV.[47] All patients received diphenhydramine 25 mg IV. There was no difference between the groups in improvement in pain intensity at 1 hour. Adverse event rates were comparable between the groups.

In the fourth class 1 study, 78 patients were randomized to metoclopramide, which was dosed in successive 20 mg doses up to 80 mg, as needed for persistent pain, or to sumatriptan 6 mg SC.[45] Patients who received metoclopramide were also treated with IV diphenhydramine. There was no difference between the groups in reduction in pain intensity, though secondary outcomes including pain freedom at 2 hours and requirement of rescue medication favored metoclopramide. Adverse events were comparable.

In a class 2 study, 27 adults were randomized to metoclopramide or dipyrone.[28] There were no differences in pain intensity at 2 hours. No significant adverse events were reported.

In a class 3 study, 91 patients were randomized to metoclopramide 0.1 mg/kg or chlorpromazine 0.1 mg/kg.[15] Efficacy and adverse events were comparable between the groups.

In a class 3 study, 113 patients were randomized to metoclopramide 10 mg IV, magnesium 2 gm IV, or placebo.[41] There were no statistically significant differences between groups with regard to pain intensity at 30 minutes. Flushing was more common in the magnesium group.

In a class 3 study, 124 patients were randomized to metoclopramide 20 mg IV or sumatriptan 6 mg SC.[46] The metoclopramide group demonstrated greater reduction in pain at 1 hour. Adverse events were not reported.

Morphine.—In a class 2 study, 190 patients were randomized to morphine 0.1 mg/kg IV or dexamethasone 8 mg IV.[20] Patients randomized to morphine reported lower pain scores at 1 hour, though the between-group difference was less than standard thresholds for clinical significance.[21] Adverse events were not reported in this study.

Octreotide.—We identified 3 randomized studies of octreotide.[48–50] In a class 1 crossover study, 43 patients were randomized to octreotide 0.1 mg SC or placebo.[49] There was no difference between the groups with regard to headache relief at 2 hours. Adverse events were comparable.

In a class 2 study, 29 patients were randomized to octreotide 0.1 mg SC or placebo.[48] The octreotide group had greater reduction in pain at 2 and 6 hours. Local reactions were more common in the octreotide group.

In another class 2 study, 44 patients were randomized to octreotide 0.1 mg IV or prochlorperazine 10 mg IV.[50] Prochlorperazine was superior with regard to patient satisfaction and reduction in pain intensity. Sedation and akathisia were more common with prochlorperazine.

Prochlorperazine.—We identified four randomized studies of prochlorperazine.[47,50–52] In a class 1 study, 66 patients were randomized to prochlorperazine 10 mg + diphenhydramine 12.5 mg IV or sumatriptan 6 mg SC.[51] There was a significantly greater decrease in pain intensity at 80 minutes in the prochlorperazine group. Restlessness was more common in the prochlorperazine group.

In a class 1 study, 77 adults were randomized to prochlorperazine 10 mg IV or metoclopramide 20 mg IV.[47] All patients received diphenhydramine 25 mg IV. There was no difference between the groups in change in pain intensity at 1 hour. Adverse event rates were comparable between the groups.

In a class 2 study, 44 patients were randomized to prochlorperazine 10 mg IV or octreotide 0.1 mg IV.[50] Prochlorperazine was superior with regard to patient satisfaction and reduction in pain intensity. Sedation and akathisia were more common with prochlorperazine.

In a class 3 study, 40 patients were randomized to prochlorperazine 10 mg IV or valproic acid 500 mg IV.[52] The prochlorperazine patients had a significantly greater decrease in pain intensity at 60 minutes. In the prochlorperazine group, 10% of patients were treated for akathisia.

Propofol.—We identified two randomized studies of propofol.[19,53] In a class 2 study, 90 patients were randomized to propofol IV or sumatriptan 6 mg SC.[53] The propofol was administered in 30–40 mg boluses with subsequent 10–20 mg boluses every 3–5 minutes up to 120 mg. At 30 minutes, there was a statistically significantly greater decrease in pain intensity in the propofol group. Chest tightness was less common in the propofol group.

In a class 3 study, 90 patients were randomized to propofol 10 mg IV, dosed every 5–10 minutes up to 80 mg or dexamethasone 0.15 mg/kg IV.[19] Patients in the propofol group reported greater decreases in pain intensity at all time points up to 45 minutes. Patients in the propofol group were very likely to report sedation. Oxygen desaturation occurred in 2 patients who received propofol.

Sumatriptan.—We identified 23 randomized trials of subcutaneous sumatriptan.[10,26,45,46,51,53–70] Fifteen placebo controlled studies revealed large and consistent statistically significant differences between sumatriptan and placebo in four class 1 studies,[64,66,68,70] seven class 2 studies,[54,56,58,60,61,63,67] and four class 3 studies.[55,57,62,65]

In a class 1 study, 66 patients were randomized to sumatriptan 6 mg SC or prochlorperazine 10 mg + diphenhydramine 12.5 mg IV.[51] There was a significantly greater decrease in pain intensity at 80 minutes in the prochlorperazine group. Restlessness was more common in the prochlorperazine group.

In another class 1 study, 78 patients were randomized to sumatriptan 6 mg SC or metoclopramide, which was dosed in successive 20 mg doses up to 80 mg, as needed for persistent pain.[45] Patients who received metoclopramide were also treated with IV diphenhydramine. There was no difference between the groups in reduction in pain intensity, though secondary outcomes including pain freedom at 2 hours and requirement of rescue medication favored metoclopramide. Adverse events were comparable.

In a third class 1 study, 40 patients were randomized to sumatriptan 6 mg SC or trimethobenzamide 200 mg IM + diphenhydramine 25 mg IM.[59] Though there were no statistically significant differences between groups, the study was underpowered and most results favored sumatriptan. The overall rate of adverse events was comparable.

A class 2 study randomized 275 adults to sumatriptan 6 mg SC, 1 gm acetylsalicylic acid, or placebo.[10] Sumatriptan and acetylsalicylic acid both outperformed placebo, while sumatriptan outperformed acetylsalicylic acid. However, the latter was tolerated as well as placebo, with significantly fewer adverse events than sumatriptan.

In another class 2 study, 90 patients were randomized to sumatriptan 6 mg SC or propofol IV.[53] The propofol was administered in 30–40 mg boluses with subsequent 10–20 mg boluses every 3–5 minutes up to 120 mg. At 30 minutes, there was a greater decrease in pain intensity in the propofol group. Chest tightness was less common in the propofol group.

A class 2 crossover study randomized 266 patients to sumatriptan 6 mg SC or to DHE 1 mg nasal spray.[69] The sumatriptan group had significantly better pain relief beginning at 15 minutes, though there were 50% fewer adverse events in the DHE group.

In a class 3 study, 124 patients were randomized to sumatriptan 6 mg SC or metoclopramide 20 mg IV.[46] The metoclopramide group demonstrated greater reduction in pain at 1 hour. Adverse events were not reported.

In another class 3 study, 310 patients were randomized to sumatriptan 6 mg SC or DHE 1 mg SC.[26] Outcomes favored sumatriptan at 1 and 2 hours though not at 3 hours. There were 305 adverse events reported among the 152 patients who received DHE and 238 adverse events among the 158 patients who received sumatriptan.

Tramadol.—A class 3 study randomized 47 patients to tramadol 100 mg IM or diclofenac 75 mg IM.[24] There were no between-group differences in any outcomes. Adverse events were uncommon.

Triamcinolone.—In a class 3 study of greater occipital nerve blocks, 37 patients were randomized to subcutaneous injections of lidocaine, bupivacaine, and 40 mg of triamcinolone or the two local anesthetics and saline.[71] Twenty minutes after the injection, there were no differences in pain scores between the groups. No adverse events were reported.

Trimethobenzamide.—In a class 1 study, 40 patients were randomized to trimethobenzamide 200 mg IM + diphenhydramine 25 mg IM or to sumatriptan 6 mg SC.[59] Although there were no statistically significant differences between groups, the study was underpowered and most results favored sumatriptan. In this study, there was no difference in the overall rate of adverse events.

Valproic Acid.—We identified four randomized studies of valproic acid.[11,17,36] In a class 1 study, 330 patients were randomized to valproate 1 gm IV, ketorolac 30 mg IV, or metoclopramide 10 mg IV.[36] Ketorolac and metoclopramide demonstrated similar efficacy with regard to headache relief at 1 hour and sustained headache relief for 48 hours, and both were superior to valproic acid. Overall adverse event rates were comparable.

A class 2 study randomized 40 adults to 1 gm of lysine acetylsalicylic acid or 800 mg of valproic acid.[11] Rates of pain relief at 1 and 24 hour sustained pain freedom were comparable between the groups. No adverse events were reported in either arm.

In a class 3 study, 40 patients were randomized to valproic acid 500 mg IV or prochlorperazine 10 mg IV.[52] The prochlorperazine patients had a significantly greater decrease in pain intensity at 60 minutes. In the prochlorperazine group, 10% of patients were treated for akathisia.

In another class 3 study, 31 patients were randomized to valproic acid 900 mg IV or dexamethasone 16 mg IV.[17] In this study, there was no difference between the groups in improvement in pain score. No adverse events were reported in this study.

Other Medications.—Hydromorphone, promethazine, and nalbuphine are each used in more than 5% of ED migraine visits annually.[1] However, these medications were not included in any clinical trials that fulfilled our selection criteria.

Do Parenteral Corticosteroids Prevent Recurrence of Migraine in Adults Discharged from an ED?—We identified three eligible RCTs in which a corticosteroid was compared to placebo and post-ED outcomes were ascertained (Table S1).[18,72,73] All three of these studies utilized dexamethasone. Two additional RCTs compared dexamethasone to active comparators. In one, dexamethasone was compared to morphine 0.1 mg/kg IV[20]; in the other to valproic acid 900 mg IV.[17]

In a class 1 study involving 115 patients, dexamethasone 24 mg IV did not outperform placebo with regard to migraine recurrence at 3 or 30 days.[72] In this study, dizziness was more common among those who received dexamethasone. In another class 1 study involving 205 patients, all patients received metoclopramide and diphenhydramine.[18] One hundred and six of these patients also received dexamethasone 10 mg IV. There were no between-group differences in the rates of sustained headache freedom 24 hours after ED discharge. Acute medication reactions were more common in the dexamethasone group. In a third class 1 study of 70 patients, dexamethasone 10 mg IV did not outperform placebo with regard to migraine recurrence within 48 hours of ED discharge.[73] Adverse events were not reported.

We performed a meta-analysis in which we aggregated data from these three placebo controlled studies. These results are presented in Figure 2. In the Friedman et al study, the primary outcome was sustained headache freedom. For the purpose of this meta-analysis, we used data provided by the authors on frequency of headache recurrence after ED discharge. When the data from these three studies were aggregated, dexamethasone decreased the frequency of headache recurrence after ED discharge (number needed to treat: 9, 95%CI: 5, 65). As can be seen in Figure 2, there was no statistical heterogeneity among the studies. All three studies reported a small but consistent

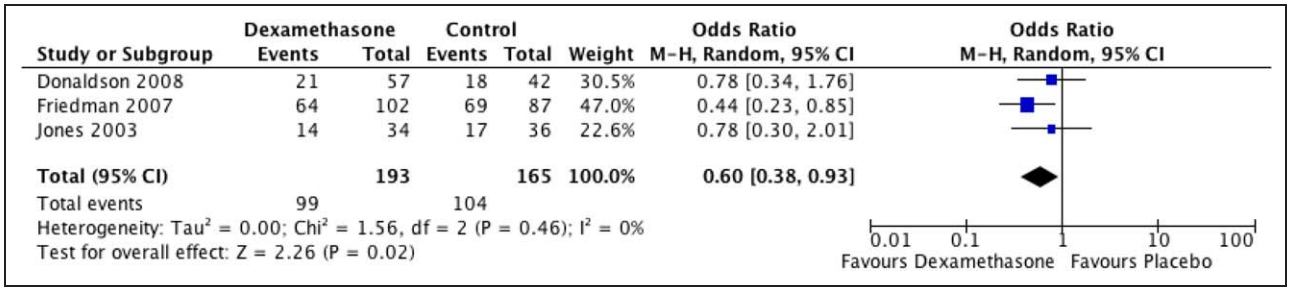

Fig. 2.—Meta-analysis of dexamethasone for headache recurrence after ED discharge. (Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.)

benefit attributable to dexamethasone. When aggregated, this result was statistically significant.

The comparison with morphine was a class 2 study, in which dexamethasone 8 mg IV demonstrated greater improvement in pain scores at 24 hours.[20] Adverse events were not reported. The comparison with valproic acid was a class 3 study, in which dexamethasone 16 mg IV resulted in comparable headache recurrence rates at 72 hours.[17] This study, too, did not report adverse events.

There were no reports in these studies of avascular necrosis, a serious adverse event linked to corticosteroid use, infections, or complications relating to loss of glycemic control. However, none of these studies were designed to detect these adverse events.

LIMITATIONS

A multitude of different methodologies were used in the studies included in this review. While the inclusion criteria were generally similar, some studies used placebo control and some used active control, some were dose-finding studies, and some used multiple active comparators. Different time points were used for the primary outcome, and different outcomes were designated as being primary or secondary. We did not identify a single outcome that was used across all studies included in this review. Some of these studies, particularly those utilizing sumatriptan, were conducted outside of the ED setting. While these disparities do not mean that the studies included in this review were unduly biased, the disparities limited our ability to aggregate data and compare results across studies. A standardized methodology for ED-based migraine studies is needed.

Furthermore, most studies included in this review did not follow patients beyond the initial treatment period. Thus, recurrence of headache after ED discharge and late developing adverse events often went unrecorded. Long-term follow-up beyond 48–72 hours was even rarer among the included studies, thus limiting our ability to comment on these.

While many studies were adequately powered for their primary outcome, they were underpowered for rare adverse events such as tardive dyskinesia or avascular necrosis. This also limits our ability to contextualize these important adverse effects with regard to frequency and severity.

CONCLUSIONS

We have identified 68 RCTs that inform the choice of injectable medical treatment of adults presenting to the ED with migraine. Five of these trials also provided evidence pertaining to the use of corticosteroids for the prevention of migraine recurrence after ED discharge. Analysis of these 68 trials provided the basis for our recommendations, listed below.

RECOMMENDATIONS

Putting the Evidence Into a Clinical Context.—When asked, migraine patients report that they want medications that take their pain away quickly and completely, without side effects and without headache recurrence.[74] However, ED migraine patients are often satisfied with modest reductions in pain.[3] While the former goal is ideal,

and should be the ultimate goal, the latter is a more likely outcome of ED treatment. It is impossible to expect that these recommendations will provide the correct therapeutic answer for every migraine patient during every ED visit. Other factors, most importantly a patient's previous experience with a particular medication, and risk of adverse events, should be considered. The following recommendations are most appropriate for a patient who has never received an injectable migraine therapeutic in the ED (Table 1).

Acute Management of Migraine.

Must Offer (Level A).—None

Should Offer (Level B).—To relieve the acute headache, intravenous **metoclopramide** should be offered to adults who present to an ED with acute migraine (Should offer–Level B). Patients should be warned about the possibility of unpleasant side effects including akathisia and drowsiness (Table 2). Irreversible adverse events have never been reported after one dose of intravenous metoclopramide.

To relieve the acute headache, intravenous **prochlorperazine** should be offered to adults who present to an ED with acute migraine (Should offer–Level B). Patients should be warned about the possibility of unpleasant side effects including akathisia and drowsiness (Table 2).

To relieve the acute headache, subcutaneous **sumatriptan** should be offered to adults who present to an ED with acute migraine (Should offer–Level B). In the ED, sumatriptan may be less efficacious than intravenous anti-dopaminergics. Sumatriptan is not appropriate for patients with contra-indications to this medication and should not be offered to those who have used ergotamine, DHE, or a triptan medication within the previous 24 hours. Unpleasant side effects have occurred in 50% of ED patients administered this medication (Table 2),[54] though irreversible adverse events in patients with low cardiovascular risk are exceedingly uncommon.

May Offer and May Avoid (Level C).

OFFER. Intravenous **acetaminophen** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

Intravenous **acetylsalicylic acid** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

Parenteral **chlorpromazine** may be offered to adults who present to an ED with acute migraine (May offer–Level C). Patients should be warned about the possibility of unpleasant side effects including orthostatic hypotension, drowsiness, and akathisia.

Intravenous **dexketoprofen** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

Intravenous **diclofenac** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

Intravenous **dipyrone** may be offered to adults who present to an ED with acute migraine (May offer–Level C), an exceedingly rare but life threatening adverse event associated with dipyrone, has resulted in elimination of this medication from the United States and other countries.

Parenteral **droperidol** may be offered to adults who present to an ED with acute migraine (May offer–Level C). Patients should be warned about the possibility of unpleasant side effects including drowsiness and akathisia, which may occur in 50% of patients. Life threatening cardiac dysrhythmias occur exceedingly rarely after administration of this medication.

Parenteral **haloperidol** may be offered to adults who present to an ED with acute migraine (May offer–Level C). Patients should be warned about the possibility of unpleasant side effects including drowsiness, and akathisia.

Intravenous **ketorolac** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

Intravenous **valproate** may be offered to adults who present to an ED with acute migraine (May offer–Level C).

AVOID. Intravenous **diphenhydramine** may be AVOIDED in adults who present to an ED with acute migraine (May avoid–Level C). The efficacy of diphenhydramine with regard to treatment of akathisia was beyond the scope of this work.

Table 1.—Evidence Supporting Recommendation

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
QUESTION 1 Which injectable medications should be considered first-line treatment for adults who present to an ED with acute migraine?					
Acetaminophen 1 gm IV	Class 1: No difference vs placebo (n = 60) Class 2: No difference vs dexketoprofen (n = 200) Class 3: No worse than rizatriptan 5 mg PO (n = 148)	Possibly effective	No serious or frequent adverse events	Well studied in a variety of pain disorders	May offer
Acetylsalicylic acid 0.5–1.8 gm IV	Class 1: None Class 2: Substantial benefit vs placebo (n = 40) Benefit vs placebo, inferior to SC sumatriptan (n = 275, 3 arms) No difference vs valproic acid (n = 40) Class 3: Benefit vs ergotamine (n = 56, crossover)	Likely effective	No serious or frequent adverse events. Better tolerated than sumatriptan	Well studied in a variety of pain conditions	May offer
Chlorpromazine 0.1–25 mg IV	Class 1: None Class 2: Benefit vs placebo (n = 60) Class 3: No difference vs metoclopramide Class 3: No difference vs ketorolac	Possibly effective	Postural hypotension and drowsiness common	None considered	May offer

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
Dexamethasone 8–16 mg IV	Class 1: No difference vs placebo (n = 205) Class 2: Benefit vs morphine (n = 190) Class 3: No difference vs valproic acid (n = 31) Inferior to propofol (n = 90)	Possibly ineffective	No serious or frequent adverse events	Avascular necrosis is a known serious adverse event attributable to corticosteroid use. It is probably associated with longer courses, higher doses, and cumulative doses. This complication has rarely been reported after isolated parenteral doses of corticosteroids Loss of glycemic control may require medical management	No recommendation
Dexketoprofen 50 mg IV	Class 1: Benefit vs placebo (n = 224) Class 2: No difference vs acetaminophen 1000 mg IV (n = 200)	Likely effective	No serious or frequent adverse events	None considered	May offer
Diclofenac 75 mg IM	Class 1: None Class 2: None Class 3: Benefit vs placebo (n = 120) No difference vs tramadol (n = 47) Mixed results vs DHE (n = 34)	Possibly effective	No serious or frequent adverse events	None considered	May offer
Dihydroergotamine 1 mg SC, IV	Class 1: None Class 2: None Class 3: Mixed results vs diclofenac (n = 34)	Possibly effective	In class 3 study, 305 adverse events among 152 patients randomized to DHE	None considered	No recommendation

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
	Mixed results vs sumatriptan (n = 310)				
Diphenhydramine 50 mg IV	Class 1: As adjuvant therapy, no difference vs placebo (n = 208)	Likely ineffective	No serious or frequent adverse events	None considered	May avoid. Considerations of efficacy, adverse events and alternate available therapies do not support routine use as a first line therapeutic in the ED
Dipyrone 1 gm IV	Class 2: No difference vs metoclopramide (n = 27) Benefit vs placebo (n = 134)	Likely effective	No serious or frequent adverse events	Agranulocytosis occurs in fewer than 1/100,000 administrations	May offer
Droperidol 2.5–8.25 mg IM	Class 1: None Class 2: Superior to placebo (n = 305) Class 3: No difference vs meperidine (n = 29)	Likely effective	In class 2 study, akathisia (31%), asthenia (25%), somnolence (20%), and anxiety (16%) were common among those who received 2.75 mg dose	Life threatening arrhythmias have occurred rarely after administration of this medication	May offer
Ergotamine 0.5 mg SC	Class 1: none Class 2: none Class 3: Inferior to acetylsalicylic acid (n = 56, crossover)	Insufficient evidence	In class 3 study, 13% had increased nausea and vomiting	None considered	No recommendation
Haloperidol 5 mg IV	Class 1: No difference vs metoclopramide Class 2: none Class 3: Superior to placebo	Likely effective	In class 1 study, no difference in adverse events vs metoclopramide. In class 3 study, 80% reported adverse events including	None considered	May offer

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
			53% with motor agitation		
Hydromorphone	Class 1: none Class 2: none Class 3: none	Insufficient evidence		In nonrandomized studies (class 4), opioids have been associated with increased frequency of recurrent ED visits and progression of the underlying migraine disorder	May avoid. Considerations of efficacy, principles of medication action, and alternate available therapies do not support routine use as a first line therapeutic in the ED.
Ketamine 0.08 mg/kg IV	Class 1: none Class 2: none Class 3: Superior to placebo (n = 17, crossover)	Insufficient evidence	Transient insobriety and fatigue were common	None considered	No recommendation
Ketorolac 30–60 mg IM, IV	Class 1: Comparable to metoclopramide, superior to valproic acid (n = 330) Class 3: No difference vs meperidine (n = 50) Class 3: Inferior to meperidine (n = 31) Class 3: No difference vs chlorpromazine	Likely effective	Well tolerated	Well studied in a variety of pain disorders	May offer
Lidocaine 1 mg/kg IV	Class 1: none Class 2: Similar to placebo (n = 25) Class 3: none	Possibly ineffective	Not reported	None considered	May avoid
Lysine clonixinate 200 mg IV	Class 1: none Class 2: none Class 3: Superior to placebo (n = 29)	Insufficient evidence	In class 3 study, adverse events more common than placebo	None considered	No recommendation

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
Magnesium 1–2 gm IV	Class 1: Inferior to placebo (all patients administered metoclopramide) (n = 44) Class 2: Superior to metoclopramide + dexamethasone (n = 70) No difference vs placebo among patients with migraine without aura. Superior to placebo among patients with migraine with aura. (n = 60) Class 3: Superior to placebo (n = 30) Comparable to placebo and metoclopramide (n = 113)	Insufficient evidence	Flushing reported in several studies	None considered	No recommendation
Meperidine 75–1.5 mg/kg IM	Class 1: none Class 2: none Class 3: No difference vs droperidol (n = 29) Superior to ketorolac 30 mg IM (n = 31) No difference vs ketorolac 60 mg IM (n = 50)	Possibly effective	No substantial differences vs active comparators in class 3 studies	In nonrandomized studies (class 4), opioids have been associated with increased frequency of recurrent ED visits and progression of the underlying migraine disorder	No recommendation
Metoclopramide 10–20 mg IV	Class 1: No difference vs sumatriptan (n = 78) No difference vs prochlorperazine (n = 77)	Highly likely to be effective	Akathisia occurs in a minority of patients. No substantial differences vs active comparators	None considered	Should offer

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
	No difference vs ketorolac, superior to valproate (n = 330) No difference vs haloperidol (n = 64) Class 2: No difference vs dipyrone (n = 27) Class 3: No difference vs chlorpromazine (n = 44) No difference vs magnesium or placebo (n = 113) Superior to sumatriptan (n = 124)				
Morphine 0.1 mg/kg IV	Class 1: none Class 2: No clinically significant difference vs dexamethasone (n = 190) Class 3: none	Possibly ineffective	Not reported in class 2 study	In non-randomized studies (class 4), opioids have been associated with increased frequency of recurrent ED visits and progression of the underlying migraine disorder	May avoid
Nalbuphine	Class 1: none Class 2: none Class 3: none	Insufficient evidence	No data available	None considered	No recommendation
Octreotide 0.1 mg SC, IV	Class 1: No difference vs placebo (n = 43) Class 2: Superior to placebo (n = 29) Inferior to prochlorperazine (n = 44) Class 3: none	Possibly ineffective	Local reactions and diarrhea reported in 20% of patients in class 1 & 2 studies	None considered	May avoid

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
Prochlorperazine 10 mg IV	Class 1: No difference vs metoclopramide (n = 77) Superior to sumatriptan (n = 66) Class 2: Superior to octreotide (n = 44) Class 3: Superior to valproate (n = 44)	Highly likely to be effective	Akathisia and drowsiness were common	None considered	Should offer
Promethazine	Class 1: none Class 2: none Class 3: none	Insufficient evidence	No data available	None considered	No recommendation
Propofol 10–40 mg IV initial bolus + 10-20 mg IV boluses	Class 1: none Class 2: Superior to sumatriptan at 30 minutes (n = 90) Class 3: Superior to dexamethasone up to 45 minutes (n = 90)	Possibly effective up to 45 minutes	In class 3 study, 44% had sedation. Oxygen desaturation occurred in 4%	Very brief duration of action	No recommendation
Sumatriptan 6 mg SC	Class 1: Comparable to metoclopramide (n = 78) No difference between trimethobenzamide but inadequately powered (n = 40) Inferior to prochlorperazine (n = 66) Superior to placebo (n = 158) Superior to placebo (n = 639) Superior to placebo (n = 51)	Highly likely to be effective	In ED-based studies, adverse events in 50% of patients	Most effective if administered very early after migraine onset	Should offer

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
	Superior to placebo (n = 577) Class 2: Superior to placebo (n = 1104) Superior to placebo and acetylsalicylic acid (n = 275) Superior to placebo (n = 277) Superior to placebo (n = 86) Superior to placebo (n = 76) Superior to placebo (n = 242) Inferior to propofol (n = 90) Superior to placebo (n = 235) Superior to placebo (n = 266) Class 3: Superior to placebo (n = 136) Superior to placebo (n = 200) Superior to placebo (n = 209) Superior to placebo (n = 170) Superior to placebo (n = 138) Inferior to metoclopramide (n = 124) Mixed outcomes vs DHE (n = 310)				
Tramadol 100 mg IM	Class 3: No differences vs diclofenac (n = 47)	Insufficient evidence	13% of patients reported adverse event in class 3 study	None considered	No recommendation

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
Triamcinolone 40 mg SC	Class 1: none Class 2: none Class 3: In study of greater occipital nerve block, no difference at 20 minutes among those randomized to triamcinolone + bupivacaine + lidocaine vs bupivacaine + lidocaine alone (n = 37)	Insufficient evidence	No adverse events reported	None considered	No recommendation
Trimethobenzamide 200 mg IM	Class 1: No difference between sumatriptan but inadequately powered (n = 40)	Insufficient evidence	5% of patients reported adverse events in class 1 study	None considered	No recommendation
Valproic Acid 500–1000 mg IV	Class 1: Inferior to ketorolac and metoclopramide (n = 330) Class 2: No difference vs acetylsalicylic acid (n = 40) Class 3: No difference vs dexamethasone (n = 31) Inferior to prochlorperazine (n = 40)	Possibly effective	Minimal adverse events	None considered	May offer
QUESTION 2 Do parenteral corticosteroids prevent recurrence of migraine in adults discharged from an ED?					
Dexamethasone 8–24 mg IV	Class 1: Meta-analysis of 3 placebo controlled class 1 studies demonstrated benefit (n = 358)	Highly likely to be effective	Dizziness and brief burning pain more common in dexamethasone group.	Avascular necrosis is a known serious adverse event attributable to corticosteroid use. It is probably associated	Should offer

Table 1.—*Continued*

Medication, Dose, Route of Administration	Summary of Evidence	Conclusion About Efficacy	Adverse Medication Effects	Principles of Medication Action	Recommendation
	Class 2: Benefit vs morphine (n = 190) Class 3: No difference vs valproic acid (n = 31)			with longer courses, higher doses, and cumulative doses. This complication has rarely been reported after isolated doses of corticosteroids. Loss of glycemic control may require medical management.	

Table 2.—Adverse Events Reported in ED-Based Trials of Parenteral Medication Given a "Should Offer" Recommendation in This Guideline

Medication	Author, year	Dose	Adverse Event	Frequency	Class of Evidence
Dexamethasone	Donaldson, 2008	24 mg IV + physician chosen acute therapeutic	Nausea/vomiting	9/56 (16%)	1
			Dizziness	9/56 (16%)	
			Mood change	3/56 (5%)	
			Swelling	2/56 (4%)	
			Muscle cramps	1/56 (2%)	
	Foroughipour, 2014	16 mg IV	None reported		3
	Friedman, 2007	10 mg IV + metoclopramide 20 mg IV + diphenhydramine 25 mg IV	Drowsiness	18/106 (17%)	1
			Dizziness	3/106 (3%)	
			Acute medication reaction	9/106 (8%)	
			Burning sensation radiating to perineum	7/106 (7%)	
	Jones, 2003	10 mg IV	None reported		1
	Soleimanpour, 2012	0.15 mg/kg IV	None reported		3
	Taheraghdam, 2011	8 mg IV	None reported		2
Metoclopramide	Cameron, 1995	0.1 mg/kg up to 3 doses IV	Drowsiness	7/29 (24%)	3
			Dizziness	4/29 (14%)	
			Dry mouth	2/29 (7%)	
			Nausea	1/29 (3%)	
			Nervousness	1/29 (3%)	
	Cete, 2005	10 mg IV	Dystonic reaction	1/37 (3%)	3
	Filho, 2006	Dose not reported	Drowsiness	2/15 (13%)	2
			Dizziness	1/15 (7%)	
	Friedman, 2005	20 mg IV (1–4 doses) + diphenhydramine 25 mg IV (1 or 2 doses)	Restlessness	2/40 (5%)	1
			Generalized weakness	5/40 (13%)	
			Drowsiness	2/40 (5%)	
			Stiffness/abnormal movements	3/40 (8%)	
	Friedman, 2007	20 mg IV (1 or 2 doses) + diphenhydramine 25 mg IV (1 or 2 doses) + placebo	Drowsiness	11/99 (11%)	1
			Dizziness	2/99 (2%)	
			Acute medication reaction	1/99 (1%)	
	Friedman, 2008	20 mg IV + diphenhydramine 25 mg IV	Drowsiness	5/38 (13%)	1
			Akathisia	2/38 (5%)	
			Generalized weakness	1/38 (3%)	
			Lightheaded	1/38 (3%)	
	Friedman, 2014	10 mg IV	Dizziness	8/109 (7%)	1
			Upper GI complaint	1/109 (1%)	

Table 2.—*Continued*

Medication	Author, year	Dose	Adverse Event	Frequency	Class of Evidence
			Restlessness (very)	6/107 (6%)	
			Too drowsy to function	2/108 (2%)	
	Gaffigan, 2015	10 mg IV + diphenhydramine 25 mg IV	Sleepiness	25/31 (81%)	1
			Restlessness	14/31 (45%)	
			Nausea	10/31 (32%)	
			Chest pain	2/31 (6%)	
	Talabi, 2013	20 mg IV	None reported		3
Prochlorperazine	Friedman, 2008	10 mg IV + diphenhydramine 25 mg IV	Drowsiness	6/39 (15%)	1
			Akathisia	3/39 (8%)	
	Kostic, 2010	10 mg IV + diphenhydramine 12.5 mg IV	Restless	9/32 (28%)	1
	Miller, 2009	10 mg IV	Akathisia	7/20 (35%)	2
	Tanen, 2003	10 mg IV	Suspected extrapyramidal reaction, received medication	2/20 (10%)	3
Sumatriptan	Akpunonu, 1995	6 mg SC	Dizziness/paresthesia	9/88 (10%)	2
			Chest symptoms	5/88 (6%)	
	Friedman, 2005	6 mg SC	Injection site reaction	1/38 (3%)	1
			Generalized weakness	9/38 (24%)	
			Drowsiness	3/38 (8%)	
			Muscle stiffness/abnormal movements	7/38 (19%)	
	Friedman, 2006	6 mg SC	Neck stiffness	3/20(15%)	1
			Drowsiness	2/20(10%)	
	Kostic, 2010	6 mg SC	None reported		1
	Moshtaghion, 2014	6 mg SC	Chest tightness	14/46 (31%)	2
			Drowsiness	2/46 (4%)	
			Hypotension	2/46 (4%)	
			Rash at injection site	15/46 (33%)	
	Talabi, 2013	6 mg SC	None reported		3

Intravenous **hydromorphone** may be AVOIDED in adults who present to an ED with acute migraine (May avoid–Level C).

Intravenous **lidocaine** may be AVOIDED in adults who present to an ED with acute migraine (May avoid–Level C).

Intravenous **morphine** may be AVOIDED in adults who present to an ED with acute migraine (May avoid–Level C).

Intravenous **octreotide** may be AVOIDED in adults who present to an ED with acute migraine (May avoid–Level C).

No Recommendation (Level U).—No recommendation can be made regarding the role of parenteral **dexamethasone** for acute migraine relief in adults who present to an ED with acute migraine (No recommendation–Level U). Please see below for our recommendation regarding dexamethasone for prevention of migraine recurrence.

No recommendation can be made regarding the role of injectable **dihydroergotamine** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of injectable **ergotamine** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of injectable **ketamine** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of injectable **lysine clonixinate** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of intravenous **magnesium** for adults who present to an ED with acute migraine (No recommendation–Level U). However, intravenous **magnesium** may be of benefit to patients who present with migraine with aura.

No recommendation can be made regarding the role of intravenous **meperidine** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of intravenous **nalbuphine** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of intravenous **propofol** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of parenteral **promethazine** for adults who present to an emergency department with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of intravenous **tramadol** for adults who present to an ED with acute migraine (No recommendation–Level U).

No recommendation can be made regarding the role of intramuscular **trimethobenzamide** for adults who present to an ED with acute migraine (No recommendation–Level U).

Prevention of Migraine Recurrence.

Must Offer (Level A).—None

Should Offer (Level B).—Parenteral dexamethasone should be offered to adults who present to an ED with acute migraine (Should offer–Level B). The ideal dose of dexamethasone is not known. The three studies included in this review used one administration of dexamethasone, which was 10 mg in one study, 20 mg in the second, and 24 mg in the third. Before prescribing dexamethasone, clinicians should consider an individual patient's risk for treatment-related adverse events (Table 2), such as loss of glycemic control in diabetics. Risk of irreversible adverse events such as avascular necrosis after one dose of dexamethasone is exceedingly low and should not dissuade clinicians from administering this medication.

May Offer (Level C).—None

Recommendations for Future Research.—In our systematic review, we identified 68 randomized trials using widely varying methodologies. Inclusion criteria, comparators, measurement instruments, duration of follow-up, and ascertainment of adverse events was often different from study to study making it difficult to compare data across studies. A number of randomized studies were excluded from this systematic review for failure to incorporate international migraine criteria into their selection

criteria. As a first recommendation for future research, we support the development of a standard methodology for ED-based headache research. Patient priorities must be understood. Patient priorities can then be used to guide the development of standardized instruments and follow-up time points.

While many patients are satisfied with the headache relief they obtain in the ED,[3] inadequate relief, adverse medication events, and recurrence of headache after ED discharge are very common. Using a standardized methodology, we hope that ED-based researchers continue to conduct and publish randomized trials of migraine therapeutics to optimize the injectable treatment that migraine patients receive in the ED.

Acknowledgments: We thank Margaret Sampson, MLIS, PhD, AHIP for developing the electronic search strategies, Helena Liu, MD, CFPC, Peter Lugomirski, MD, FRCPC, Erick Sell, MD, Daniela Pohl, MD, and Carolina Rush, MD, FRCPC for their assistance with translation, the American Headache Society Guideline Committee for their oversight, and Linda McGillicuddy for logistical assistance.

STATEMENT OF AUTHORSHIP

The American Headache Society guideline committee determined the need for a guideline statement on this topic. Deborah Tepper assembled a panel of AHS members with the expertise required to develop this guideline. All authors developed the relevant clinical question statements and outlined the search strategy. Serena L. Orr, Benjamin W. Friedman, and Suzanne Christie selected abstracts for inclusion, abstracted the data, and graded the quality of each study. All authors synthesized the evidence and developed recommendations. Serena L. Orr and Benjamin W. Friedman drafted the manuscript. All authors edited the manuscript for content and style.

REFERENCES

1. Friedman BW, West J, Vinson DR, Minen MT, Restivo A, Gallagher EJ. Current management of migraine in US emergency departments: An analysis of the National Hospital Ambulatory Medical Care Survey. *Cephalalgia.* 2015;35:301-309.
2. Vinson DR. Treatment patterns of isolated benign headache in US emergency departments. *Ann Emerg Med.* 2002;39:215-222.
3. Friedman BW, Bijur PE, Lipton RB. Standardizing emergency department-based migraine research: An analysis of commonly used clinical trial outcome measures. *Acad Emerg Med.* 2010; 17:72-79.
4. The American Academy of Neurology. *Clinical Practice Guideline Process Manual*, 2011 edition. St. Paul, MN: The American Academy of Neurology; 2011.
5. Olesen J, Bendtsen L, Dodick D, et al. The international classification of headache disorders, 3rd edition (beta version). *Cephalalgia.* 2013;33:629-808.
6. National Center for Health Statistics. Ambulatory health care data. Available at: http://www.cdc.gov/nchs/ahcd.htm. Accessed 25 September 2015.
7. Zhang A, Jiang T, Luo Y, et al. Efficacy of intravenous propacetamol hydrochloride in the treatment of an acute attack of migraine. *Eur J Intern Med.* 2014;25:629-632.
8. Leinisch E, Evers S, Kaempfe N, et al. Evaluation of the efficacy of intravenous acetaminophen in the treatment of acute migraine attacks: A double-blind, placebo-controlled parallel group multicenter study. *Pain.* 2005;117:396-400.
9. Turkcuer I, Serinken M, Eken C, et al. Intravenous paracetamol versus dexketoprofen in acute migraine attack in the emergency department: A randomised clinical trial. *Emerg Med J.* 2014;31: 182-185.
10. Diener HC. Efficacy and safety of intravenous acetylsalicylic acid lysinate compared to subcutaneous sumatriptan and parenteral placebo in the acute treatment of migraine. A double-blind, double-dummy, randomized, multicenter, parallel group study. The ASASUMAMIG Study Group. *Cephalalgia.* 1999;19:581-588. discussion 542.
11. Leniger T, Pageler L, Stude P, Diener HC, Limmroth V. Comparison of intravenous valproate with intravenous lysine-acetylsalicylic acid in acute migraine attacks. *Headache.* 2005;45:42-46.

12. Limmroth V, Katsarava Z, Diener HC. Acetylsalicylic acid in the treatment of headache. *Cephalalgia.* 1999;19:545-551.
13. Taneri Z, Petersen-Braun M. Double blind study of intravenous aspirin vs placebo in the treatment of acute migraine attacks. *Schmerz.* 1995;9:124-129.
14. Bigal ME, Bordini CA, Speciali JG. Intravenous chlorpromazine in the emergency department treatment of migraines: A randomized controlled trial. *J Emerg Med.* 2002;23:141-148.
15. Cameron JD, Lane PL, Speechley M. Intravenous chlorpromazine vs intravenous metoclopramide in acute migraine headache. *Acad Emerg Med.* 1995; 2:597-602.
16. Shrestha M, Singh R, Moreden J, Hayes JE. Ketorolac vs chlorpromazine in the treatment of acute migraine without aura. A prospective, randomized, double-blind trial. *Arch Intern Med.* 1996;156:1725-1728.
17. Foroughipour M, Ghandehari K, Khazaei M, Ahmadi F, Shariatinezhad K, Ghandehari K. Randomized clinical trial of intravenous valproate (orifil) and dexamethasone in patients with migraine disorder. *Iran J Med Sci.* 2013;38:150-155.
18. Friedman BW, Greenwald P, Bania TC, et al. Randomized trial of IV dexamethasone for acute migraine in the emergency department. *Neurology.* 2007;69:2038-2044.
19. Soleimanpour H, Taheraghdam A, Ghafouri RR, Taghizadieh A, Marjany K, Soleimanpour M. Improvement of refractory migraine headache by propofol: Case series. *Int J Emerg Med.* 2012;5:19.
20. Taheraghdam AA, Amiri H, Shojaan H, Shamsvahdati S, Houshyar Y. Intravenous dexamethasone versus morphine in relieving of acute migraine headache. *Pak J Biol Sci.* 2011;14:682-687.
21. Todd KH, Funk JP. The minimum clinically important difference in physician-assigned visual analog pain scores. *Acad Emerg Med.* 1996;3:142-146.
22. Gungor F, Akyol KC, Kesapli M, et al. Intravenous dexketoprofen vs placebo for migraine attack in the emergency department: A randomized, placebo-controlled trial. *Cephalalgia.* 2016;36:179–184.
23. Bigal ME, Bordini CA, Speciali JG. Intramuscular diclofenac in the acute treatment of migraine: A double-blind placebo controlled study. *Arq Neuropsiquiatr.* 2002;60:410-415.
24. Engindeniz Z, Demircan C, Karli N, et al. Intramuscular tramadol vs. diclofenac sodium for the treatment of acute migraine attacks in emergency department: A prospective, randomised, double-blind study. *J Headache Pain.* 2005;6:143-148.
25. Jovicic A, Maric D, Ilic T. Treatment of acute migraine attacks. *Vojnosanit Pregl.* 1995;52:44-48.
26. Winner P, Ricalde O, Le Force B, Saper J, Margul B. A double-blind study of subcutaneous dihydroergotamine vs subcutaneous sumatriptan in the treatment of acute migraine. *Arch Neurol.* 1996;53: 180-184.
27. Friedman BW, Cabral L, Adewunmi V, et al. Diphenhydramine as adjuvant therapy for acute migraine: An emergency department-based randomized clinical trial. *Ann Emerg Med.* 2016;67: 32-39.
28. Filho SMMF, Costa MS, Fernandes MT, Foerster MV. Comparação de dipirona intravenosa com metoclopramida intravenosa no tratamento de crise aguda de enxaqueca: Ensaio clínico randomizado. *Arq Neuropsiquiatr.* 2006;64:1005-1008.
29. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous dipyrone in the acute treatment of migraine without aura and migraine with aura: A randomized, double blind, placebo controlled study. *Headache.* 2002;42:862-871.
30. Silberstein SD, Young WB, Mendizabal JE, Rothrock JF, Alam AS. Acute migraine treatment with droperidol: A randomized, double-blind, placebo-controlled trial. *Neurology.* 2003;60:315-321.
31. Richman PB, Allegra J, Eskin B, et al. A randomized clinical trial to assess the efficacy of intramuscular droperidol for the treatment of acute migraine headache. *Am J Emerg Med.* 2002;20:39-42.
32. Gaffigan ME, Bruner DI, Wason C, Pritchard A, Frumkin K. A randomized controlled trial of intravenous haloperidol vs. intravenous metoclopramide for acute migraine therapy in the emergency department. *J Emerg Med.* 2015;49:326-334.
33. Honkaniemi J, Liimatainen S, Rainesalo S, Sulavuori S. Haloperidol in the acute treatment of migraine: A randomized, double-blind, placebo-controlled study. *Headache.* 2006;46:781-787.
34. Nicolodi M, Sicuteri F. Exploration of NMDA receptors in migraine: Therapeutic and theoretic implications. *Int J Clin Pharmacol Res.* 1995;15: 181-189.

35. Duarte C, Dunaway F, Turner L, Aldag J, Frederick R. Ketorolac versus meperidine and hydroxyzine in the treatment of acute migraine headache: A randomized, prospective, double-blind trial. *Ann Emerg Med.* 1992;21:1116-1121.
36. Friedman BW, Garber L, Yoon A, et al. Randomized trial of IV valproate vs metoclopramide vs ketorolac for acute migraine. *Neurology.* 2014;82: 976-983.
37. Larkin GL, Prescott JE. A randomized, double-blind, comparative study of the efficacy of ketorolac tromethamine versus meperidine in the treatment of severe migraine. *Ann Emerg Med.* 1992;21:919-924.
38. Reutens DC, Fatovich DM, Stewart-Wynne EG, Prentice DA. Is intravenous lidocaine clinically effective in acute migraine? *Cephalalgia.* 1991;11: 245-247.
39. Krymchantowski AV, Silva MT. Intravenous lysine clonixinate for the acute treatment of severe migraine attacks: A double-blind, randomized, placebo-controlled study. *Curr Ther Res Clin Exp.* 2003;64:505-513.
40. Bigal ME, Bordini CA, Tepper SJ, Speciali JG. Intravenous magnesium sulphate in the acute treatment of migraine without aura and migraine with aura. A randomized, double-blind, placebo-controlled study. *Cephalalgia.* 2002;22:345-353.
41. Cete Y, Dora B, Ertan C, Ozdemir C, Oktay C. A randomized prospective placebo-controlled study of intravenous magnesium sulphate vs. metoclopramide in the management of acute migraine attacks in the emergency department. *Cephalalgia.* 2005;25:199-204.
42. Corbo J, Esses D, Bijur PE, Iannaccone R, Gallagher EJ. Randomized clinical trial of intravenous magnesium sulfate as an adjunctive medication for emergency department treatment of migraine headache. *Ann Emerg Med.* 2001;38:621-627.
43. Zadeh AAA. Efficacy of intravenous magnesium sulfate in acute attacks of migraine. *J Headache Pain.* 2010;11:S92.
44. Shahrami A, Assarzadegan F, Hatamabadi HR, Asgarzadeh M, Sarehbandi B, Asgarzadeh S. Comparison of therapeutic effects of magnesium sulfate vs. dexamethasone/metoclopramide on alleviating acute migraine headache. *J Emerg Med.* 2015;48:69-76.
45. Friedman BW, Corbo J, Lipton RB, et al. A trial of metoclopramide vs sumatriptan for the emergency department treatment of migraines. *Neurology.* 2005;64:463-468.
46. Talabi S, Masoumi B, Azizkhani R, Esmailian M. Metoclopramide versus sumatriptan for treatment of migraine headache: A randomized clinical trial. *J Res Med Sci.* 2013;18:695-698.
47. Friedman BW, Esses D, Solorzano C, et al. A randomized controlled trial of prochlorperazine versus metoclopramide for treatment of acute migraine. *Ann Emerg Med.* 2008;52:399-406.
48. Kapicioglu S, Gokce E, Kapicioglu Z, Ovali E. Treatment of migraine attacks with a long-acting somatostatin analogue (octreotide, SMS 201-995). *Cephalalgia.* 1997;17:27-30.
49. Levy MJ, Matharu MS, Bhola R, Meeran K, Goadsby PJ. Octreotide is not effective in the acute treatment of migraine. *Cephalalgia.* 2005;25: 48-55.
50. Miller MA, Levsky ME, Enslow W, Rosin A. Randomized evaluation of octreotide vs prochlorperazine for ED treatment of migraine headache. *Am J Emerg Med.* 2009;27:160-164.
51. Kostic MA, Gutierrez FJ, Rieg TS, Moore TS, Gendron RT. A prospective, randomized trial of intravenous prochlorperazine versus subcutaneous sumatriptan in acute migraine therapy in the emergency department. *Ann Emerg Med.* 2010;56:1-6.
52. Tanen DA, Miller S, French T, Riffenburgh RH. Intravenous sodium valproate versus prochlorperazine for the emergency department treatment of acute migraine headaches: A prospective, randomized, double-blind trial. *Ann Emerg Med.* 2003;41: 847-853.
53. Moshtaghion H, Heiranizadeh N, Rahimdel A, Esmaeili A, Hashemian H, Hekmatimoghaddam S. The efficacy of propofol vs. subcutaneous sumatriptan for treatment of acute migraine headaches in the emergency department: A double-blinded clinical trial. *Pain Pract.* 2015;15:701-705.
54. Akpunonu BE, Mutgi AB, Federman DJ, et al. Subcutaneous sumatriptan for treatment of acute migraine in patients admitted to the emergency department: A multicenter study. *Ann Emerg Med.* 1995;25:464-469.
55. Burke-Ramirez P, Asgharnejad M, Webster C, Davis R, Laurenza A. Efficacy and tolerability of subcutaneous sumatriptan for acute migraine: A

comparison between ethnic groups. *Headache.* 2001;41:873-882.

56. Cady RK, Wendt JK, Kirchner JR, Sargent JD, Rothrock JF, Skaggs H Jr. Treatment of acute migraine with subcutaneous sumatriptan. *JAMA.* 1991;265:2831-2835.
57. Cady RK, Dexter J, Sargent JD, Markley H, Osterhaus JT, Webster CJ. Efficacy of subcutaneous sumatriptan in repeated episodes of migraine. *Neurology.* 1993;43:1363-1368.
58. Ensink FB. Subcutaneous sumatriptan in the acute treatment of migraine. Sumatriptan International Study Group. *J Neurol.* 1991;238 (Suppl 1):S66-S69.
59. Friedman BW, Hochberg M, Esses D, et al. A clinical trial of trimethobenzamide/diphenhydramine versus sumatriptan for acute migraines. *Headache.* 2006;46:934-941.
60. Gross ML, Kay J, Turner AM, Hallett K, Cleal AL, Hassani H. Sumatriptan in acute migraine using a novel cartridge system self-injector. United Kingdom Study Group. *Headache.* 1994;34:559-563.
61. Henry P, d'Allens H. Subcutaneous sumatriptan in the acute treatment of migraine in patients using dihydroergotamine as prophylaxis. French Migraine Network Bordeaux-Lyon-Grenoble. *Headache.* 1993;33:432-435.
62. Jensen K, Tfelt-Hansen P, Hansen EW, Krois EH, Pedersen OS. Introduction of a novel self-injector for sumatriptan. A controlled clinical trial in general practice. *Cephalalgia.* 1995;15:423-429.
63. Mathew NT, Dexter J, Couch J, et al. Dose ranging efficacy and safety of subcutaneous sumatriptan in the acute treatment of migraine. US Sumatriptan Research Group. *Arch Neurol.* 1992; 49:1271-1276.
64. Mushet GR, Cady RK, Baker CC, Clements B, Gutterman DL, Davis R. Efficacy and tolerability of subcutaneous sumatriptan administered using the IMITREX STATdose System. *Clin Ther.* 1996; 18:687-699.
65. Russell MB, Holm-Thomsen OE, Rishoj Nielsen M, Cleal A, Pilgrim AJ, Olesen J. A randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia.* 1994;14:291-296.
66. Treatment of migraine attacks with sumatriptan. The Subcutaneous Sumatriptan International Study Group. *N Engl J Med.* 1991;325:316-321.
67. Self-treatment of acute migraine with subcutaneous sumatriptan using an auto-injector device. The Sumatriptan Auto-Injector Study Group. *Eur Neurol.* 1991;31:323-331.
68. Thomson AN, Arthur GP, Bergin PS, et al. Subcutaneous sumatriptan in acute treatment of migraine: A multicentre New Zealand trial. *N Z Med J.* 1993;106:171-173.
69. Touchon J, Bertin L, Pilgrim AJ, Ashford E, Bes A. A comparison of subcutaneous sumatriptan and dihydroergotamine nasal spray in the acute treatment of migraine. *Neurology.* 1996;47:361-365.
70. Wendt J, Cady R, Singer R, et al. A randomized, double-blind, placebo-controlled trial of the efficacy and tolerability of a 4-mg dose of subcutaneous sumatriptan for the treatment of acute migraine attacks in adults. *Clin Ther.* 2006;28:517-526.
71. Ashkenazi A, Levin M. Greater occipital nerve block for migraine and other headaches: Is it useful? *Curr Pain Headache Rep.* 2007;11:231-235.
72. Donaldson D, Sundermann R, Jackson R, Bastani A. Intravenous dexamethasone vs placebo as adjunctive therapy to reduce the recurrence rate of acute migraine headaches: A multicenter, double-blinded, placebo-controlled randomized clinical trial. *Am J Emerg Med.* 2008;26:124-130.
73. Jones JS, Brown MD, Bermingham M. Efficacy of parenteral dexamethasone to prevent relapse after ED treatment of acute migraine. *Acad Emerg Med.* 2003;10:542.

74. Lipton RB, Hamelsky SW, Dayno JM. What do patients with migraine want from acute migraine treatment? *Headache.* 2002;42 (Suppl 1):3-9.

APPENDIX 1: CLASSIFICATION OF EVIDENCE FOR THERAPEUTIC TRIALS[4]

Class	Criteria
1	- Randomized, controlled clinical trial (RCT) in a representative population - Masked or objective outcome assessment - Relevant baseline characteristics are presented and substantially equivalent between treatment groups, or there is appropriate statistical adjustment for differences
2	- RCT that lacks one or two criteria b–d (see Class 1) - All relevant baseline characteristics are presented and substantially equivalent among treatment groups, or there is appropriate statistical adjustment for differences - Masked or objective outcome assessment
3	- All other RCTs

Appendix (Continued)

Class	Criteria
	- Also required: a. Concealed allocation b. Primary outcome(s) clearly defined c. Exclusion/inclusion criteria clearly defined d. Adequate accounting for dropouts (with at least 80% of enrolled subjects completing the study)

RCT = randomized controlled trial.

APPENDIX 2: CLASSIFICATION OF RECOMMENDATIONS LEVEL[52]

Recommendation Level	Level U	Level C	Level B	Level A
Wording	None	May	Should	Must
Value of benefit relative to risk	Too close to call	Small	Moderate	Large
Confidence in evidence	Very Low	Low	Moderate	High
Strength of principle-based inferences	Not plausible	Plausible	Convincing	Compelling

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Fig. S1. Search strategy.

Table S1. Summary of Studies