Effectiveness and Safety of Pharmacologic Therapies for Migraine in the Emergency Department: A Systematic Review and Bayesian Network Meta-analysis

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Study objective: We performed a systematic review and Bayesian network meta-analysis to determine which pharmacologic therapies are relatively more effective and safer for migraine in adult patients who present to the emergency department (ED).

Methods: We searched MEDLINE, Embase, and Web of Science from inception to February 9, 2024. Eligible studies were randomized controlled trials that enrolled adult participants presenting to ED with migraine and compared one pharmacologic therapy to another or placebo. Outcomes were as follows: 1) adequate pain relief at 2 hours, 2) change in pain intensity at 1 hour, 3) need for rescue drug at 2 hours, and 4) significant adverse reaction. We extracted data according to PRISMA-network meta-analysis and appraised trials using Cochrane RoB 2. For dichotomous outcomes, we performed Bayesian network meta-analysis to calculate odds ratios with 95% credible intervals; for continuous outcomes, we performed frequentist network meta-analysis to calculate mean differences with 95% confidence intervals. We assessed confidence using Confidence in Network Meta-analysis. We used Surface under the cumulative ranking curve (SUCRA) to rank agents.

Results: Chlorpromazine intravenous (IV)/intramuscular (IM) (SUCRA=87.3%) was most likely to be superior for "adequate pain relief at 2 hours" (24 trials; n=2,361); metoclopramide IV-ibuprofen IV (SUCRA=94.6%) was most likely to be superior for "need for rescue drug" (not needing rescue drug) at 2 hours (27 trials; n=2,942); dexamethasone IV (SUCRA=79.5%) was most likely to be superior for "significant adverse reaction" (not causing adverse reaction) (22 trials; n=2,450). The network for change in pain intensity demonstrated statistically significant incoherence at the overall level. Confidence in network meta-analysis estimates (certainty of evidence) varied and was mostly "low" or "very low," limiting the validity of the probabilistic analyses.

Conclusions: According to Bayesian network meta-analysis, ibuprofen IV is definitely among the least effective for adequate pain relief; chlorpromazine IV/IM is definitely among the most effective; valproate IV is definitely among the least effective, and ketorolac IV/IM is possibly among the least effective as single agents. The relative safety of the pharmacologic therapies cannot be determined with sufficient certainty. [Ann Emerg Med. 2025;85:313-329.]

Please see page 314 for the Editor's Capsule Summary of this article.

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INTRODUCTION

Background

Migraine is the most common etiology in adult patients presenting to the emergency department (ED) for headache, accounting for one-third of visits with an estimated 1-year prevalence of approximately 15%.[1,2] Migraine is also a leading cause of disability worldwide.[3] Although the exact pathophysiology is incompletely understood, the trigeminal nerve and its projections to the intracranial vasculature likely play an important role. Activation of the trigeminovascular system results in the release of various vasoactive peptides (such as calcitonin gene-related peptide) and induction of a local inflammatory response.[4] Based on the presumed pathogenesis of migraine, various classes of therapeutic agents have been studied for pain relief, including nonsteroidal anti-inflammatory drugs (NSAID), triptans, selective serotonin 5-HT_{1F} receptor agonists, and calcitonin gene-related peptide-receptor antagonists.[4] Other commonly used agents in the ED have included a variety of antiemetics, neuroleptics, and antiepileptics. Use of these agents for acute migraine is also supported by the American Headache Society practice guidelines.[5,6] Two nationally representative studies on the

Editor's Capsule Summary

What is already known on this topic

Multiple drugs are available to treat acute migraine.

What question this study addressed

Studies often compare pairs of drugs to each other or to placebo, but it is not clear which drugs are most effective in the emergency department.

What this study adds to our knowledge

In a Bayesian network meta-analysis of randomized controlled trials, intravenous chlorpromazine and possibly metoclopramide-NSAID combinations were most likely to be among the most effective drugs.

How this is relevant to clinical practice

This analysis gives providers a basis for choosing medications to treat migraine in the emergency department.

management of migraine in EDs from 2010 to 2017 found that most patients were treated with antiemetics, NSAIDs, diphenhydramine, and opioids.[1,7] However, the optimal pharmacologic therapy for acute migraine management in the ED remains a topic of debate.

Importance

Rapid relief of migraine in the ED is of utmost importance to both patients and clinicians. Traditional meta-analyses have compared single agents or combinations with each other or with placebo.[8-12] A recent frequentist network meta-analysis included data from non-ED settings, compared drug classes, and did not perform a confidence assessment.[13] A Bayesian network meta-analysis provides a posterior distribution of all relative treatment effects between the interventions in the network and allows for probability statements for a particular outcome.[14] The Bayesian approach may, therefore, be more appropriate than a frequentist one when the goal is to make a medical decision and predict the outcome under some degree of uncertainty.[15]

Goals of This Investigation

We aimed to conduct Bayesian network meta-analysis of individual pharmacologic therapies used to achieve rapid pain relief in adult patients presenting to the ED with migraine to determine which are relatively more effective and safer. We hope that this study will better inform emergency clinicians about the selection of pharmacologic therapy for managing ED patients with acute migraine.

MATERIALS AND METHODS

Study Design

The protocol for the original systematic review was registered in the International Prospective Register of Systematic Reviews (PROSPERO: CRD42021252424), available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021252424. We adhered to the Preferred Reporting Items for Systematic Reviews and Network Meta-Analysis statement (PRISMA-network meta-analysis).[16] The completed PRISMA-network meta-analysis checklist is Appendix E1 (available at http://www.annemergmed.com).

Eligibility Criteria

We limited studies to randomized controlled trials and used a "PICOS" (Population, Intervention, Comparison, Outcome, Setting) method to determine eligibility of studies for inclusion. We excluded observational studies, case series, case reports, and animal studies, as the analysis of nonrandomized data would significantly limit the quality of the network meta-analysis results. We also excluded non-English language articles and studies of complementary, alternative, and integrative medicines. We did not exclude studies based on migraine criteria, frequency, duration, or type.

Population: Adult participants (age 18 years and older) presenting to an ED with migraine and requiring pharmacologic therapy

Intervention: Single pharmacologic agent or combination of pharmacological agents

Comparison: Another pharmacologic agent, combination of pharmacologic agents, or placebo

Outcomes: 1) adequate pain relief as defined by the individual trial at 2 hours, 2) change in pain intensity at 1 hour, 3) need for rescue drug at 2 hours, and 4) significant adverse reaction – sedation, akathisia, dystonia, hypotension

Setting: General ED

We selected studies that reported pain intensity assessments between 30 and 120 minutes after drug administration, a time frame consistent with International Headache Society research guidelines and suitable for examining the effectiveness of a pharmacologic therapy within an ED visit.[17] The selection of studies with various endpoints could have introduced time of assessment as a potential effect modifier and a potential source of intransitivity, particularly for the change in pain intensity outcome. The assumption of transitivity is fundamental to the validity of network meta-analysis. To maximize the plausibility of transitivity, we selected a range of 30 to 60

minutes within which to extract change in pain intensity data. To strengthen the network, we aggregated data from study arms with different dosing regimens of the same agent. Except for the significant adverse reaction outcome, we aggregated data from study arms given the same agent by different parenteral routes, reasoning that the analgesic effect, regardless of route, would be similar at 30 minutes ("Pharmacodynamic Characteristics of Drug Effect by Route of Administration" is in Appendix E2, available at http://www.annemergmed.com). We also aggregated data from study arms with nerve blocks using either bupivacaine or lidocaine, provided the site of the nerve block was consistent. Von Boxstael et al[18] found no clinically significant difference in effect onset or duration between lidocaine 2% and bupivacaine 0.5% when used in wrist blocks. Where an individual trial included more than one intervention arm with the same agent administered in different doses, we combined the outcome data.[19] We also assumed that an intravenous crystalloid bolus and antihistamine administration do not influence effectiveness. Jones et al[20] examined the combination of 1 L normal saline solution bolus with prochlorperazine IV versus prochlorperazine IV alone and showed no statistically significant treatment effect from the normal saline solution bolus. The American Headache Society guidelines do not specifically address intravenous hydration as a therapy.[5] Friedman et al[21] examined diphenhydramine IV as adjuvant therapy added to metoclopramide IV and found no difference in analgesia outcomes. American Headache Society Guidelines state that diphenhydramine IV is "likely ineffective" and "considerations of efficacy, adverse events, and alternate available therapies do not support routine use as a first-line therapeutic in the ED."[5] We did acknowledge, however, that an antihistamine could influence the occurrence of significant adverse reactions, particularly akathisia and dystonia, and separated data from drug combinations that included an antihistamine for the significant adverse reaction outcome. Differences were resolved by consensus, and all authors agreed on the final group of included articles.

Information Sources and Search Strategy

A medical librarian (J.K.) searched MEDLINE (Ovid), Embase (Ovid), Cumulated Index to Nursing and Allied Health Literature, Web of Science, Cochrane Database of Systematic Reviews, and Cochrane Central Register of Controlled Trials to identify relevant studies published from inception to February 9, 2024. The search encompassed the grey literature, and we supplemented the search using the snowballing method by manually reviewing the references list of included studies and systematic reviews on similar topics. We adhered to the Preferred Reporting Items for Systematic reviews and Meta-Analyses literature Search extension.[22] The detailed search strategy is presented in Appendix E2.

Study Selection

Two authors (I.d. and A.J.S.) independently reviewed titles and abstracts from the combined database search and selected articles for full-text review based upon prespecified eligibility. The same authors then independently reviewed the full texts and came to a consensus on the final group of included articles.

Data Collection

Using a structured data form, 3 authors (I.d., J.B., and N.A.) independently extracted from all included studies the type of population, number of participants, age, sex, migraine type, therapeutic agent(s), control agent(s), proportion with adequate pain relief at 30 to 120 minutes, change in pain intensity at 30 to 60 minutes, proportion that needed rescue drug at 30 to 120 minutes, and significant adverse reaction (sedation, akathisia, dystonia, and hypotension). Data collection also incorporated study design, methodology, drug dosing, and route of drug administration. "Additional Details of Data Collection" is in Appendix E2. When data were unavailable or unclear in the original papers, we contacted the corresponding authors for complete data and clarification. When necessary, we extracted data from figures or graphs in the included articles using WebPlotDigitizer software version 4.6 (https://automeris.io/WebPlotDigitizer; Pacifica).[23] We resolved any discrepancies by discussion and consensus.

Geometry of the Network

We analyzed data from published randomized controlled trials performed on adult participants who presented to the ED with migraine. In the evidence network of pharmacologic therapies, each therapy is represented by a node, and randomized comparisons between therapies are shown by links between the nodes. We expected that the networks could be derived from a limited number of studies and have nodes (pharmacologic therapies) with varying connectedness (direct evidence) and magnitude (pooled sample size). A sparse network with fewer connections and smaller nodes will depend greatly on indirect evidence in smaller quantities and limit the strength of its meta-analysis.

Risk of Bias Within Individual Studies

Two investigators (N.A. and R.A.) independently assessed the risk of bias within all included studies at the outcome level using Version 2 of the Cochrane tool for assessing risk of bias in randomized trials (RoB 2).[24] "Additional Details of the Risk of Bias Assessment" is in Appendix E2.

Summary Measures

We report pairwise comparisons (network meta-analysis estimates) using a league table, with each pairwise comparison reported as an odds ratio (OR) with a 95% credible interval (95% CrI). We present the probabilistic analysis results using the Surface Under the Cumulative Ranking Curve (SUCRA), a numeric presentation of the overall ranking based on the probability that a therapy was the most effective or safest. We also present the cumulative rankograms that underlie the SUCRA. Further explanation of "Network Meta-Analysis Concepts" is in Appendix E2.

Planned Methods of Data Analysis

For the dichotomous outcomes of adequate pain relief at 2 hours, need for rescue drug at 2 hours, and significant adverse reaction, we conducted a Bayesian network meta-analysis using a Markov Chain Monte Carlo method with a random-effects model and vague prior distribution. We performed the analysis using WinBUGS 1.4.3 (MRC Biostatistics Unit, Cambridge, United Kingdom) and NetMetaXL 1.6.1 (Canadian Agency for Drugs and Technologies in Health, Ottawa, Canada).[25,26] For the continuous outcome of change in pain intensity at 1 hour, we conducted a frequentist network meta-analysis using Stata/SE v18.0 (StataCorp LLC, College Station, TX).[27] We performed a confidence assessment of the network meta-analysis estimates using the Confidence in Network Meta-analysis framework and web application.[28,29] The confidence assessment of each network meta-analysis estimate determined the certainty of evidence for the corresponding pairwise comparison (eg, moderate confidence = moderate certainty of evidence). "Additional Details of the Data Analysis" and "Additional Details of the Confidence Assessment" are in Appendix E2.

RESULTS

Study Selection

The study selection process is presented in Figure 1. Sixty-four trials remained eligible. "Additional Details of Full Text Review for Eligibility" is in Appendix E2.[21,30-92]

Summary of the Network Geometry

Twenty-four trials that randomly assigned 2,361 participants remained for "adequate pain relief"; 24 trials that randomly assigned 2,696 participants remained for "change in pain intensity"; 27 trials that randomly assigned 2,942 participants remained for "need for rescue drug"; 22 trials that randomly assigned 2,450 participants remained for "significant adverse reaction."[21,31,33,35,37-39,41-45,47-50,54,56-66,68-75,78,83,84,86-92] The evidence network configurations are presented in Figures 2A, B and C. Among the networks, 21% to 26% of pairwise comparisons included direct evidence, and there was some imbalance in evidence among the therapies. "Additional Details of Summary of the Network Geometry" is in Appendix E2.

Study Characteristics

For each of the data syntheses, there was some variation among the trials, particularly in their inclusion/exclusion criteria, proportion of female participants, and migraine type. For example, all but 4 studies enrolled participants using varying iterations of the International Headache Society or similarly defined criteria, and 12 trials enrolled only participants with a prespecified, initial level of pain intensity.[21,31,33,39,59-61,63,71-75,83,84] The selected studies also varied in individual drug regimens, definition of adequate pain relief, pain scale, and meticulousness of monitoring for adverse reactions. "Additional Details of Study Characteristics" is in Appendix E2. The description of all eligible studies (including those that could not be included in any network) is detailed comprehensively in Table E1 (see Appendix E3, available at http://www.annemergmed.com).

Risk of Bias Within Individual Studies

Among the trials whose data were analyzed, there were primarily "some concerns" with selection of the reported result. The assessment of risk of bias within each of the individual studies for network meta-analysis at the outcome level is summarized in Figures E1, E3, and E5 (see Appendix E4, available at http://www.annemergmed.com).

Synthesis of Results

Adequate Pain Relief at 2 Hours. The network meta-analysis found with moderate certainty that 4 agents in comparison to placebo are associated with increased likelihood of adequate pain relief at 2 hours: chlorpromazine IV/IM (OR 9.79, 95% CrI 3.42 to 24.42), prochlorperazine IV/IM (OR 8.10, 95% CrI 2.91 to 22.44), propofol (OR 5.77, 95% CrI 1.45 to 24.04), and metoclopramide IV/IM (OR 3.91, 95% CrI 1.93 to 8.11).

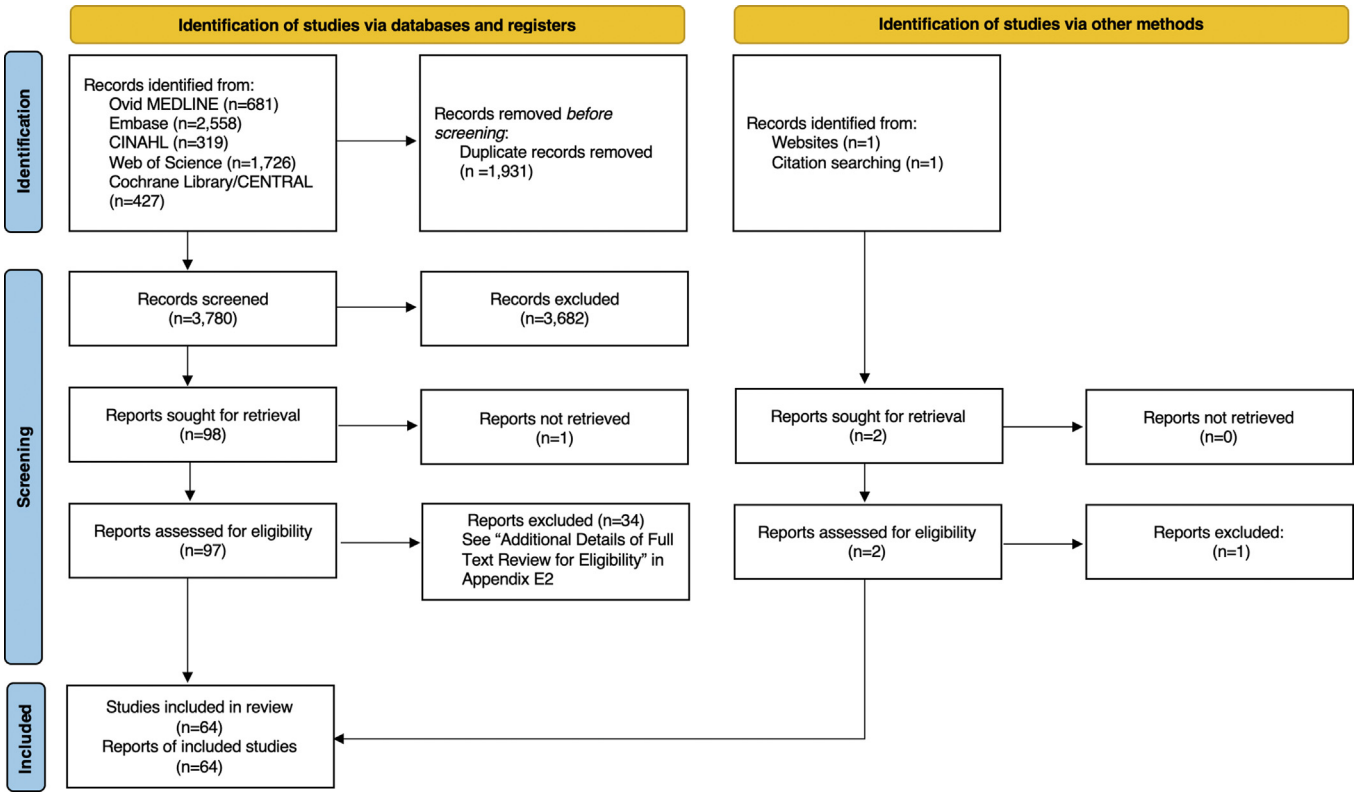

Figure 1. PRISMA flow diagram. From: Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. https://doi.org/10.1136/bmj.n71 *CENTRAL*, Cochrane Central Register of Controlled Trials; CINAHL, Cumulated Index to Nursing and Allied Health Literature.

The network meta-analysis estimates of all pairwise comparisons are in Table E2 (see Appendix E3, available at http://www.annemergmed.com). The summary of the risk of bias is illustrated in Figure 3A. There was no evidence of incoherence at the overall level (Table E2 [see Appendix E3]) or among any of the pairwise comparisons (Figure E2 [see Appendix E4]). Confidence in the effect estimates was variable: 64 estimates (61%) rated "very low," 25 (24%) rated "low," 15 (14%) rated "moderate," and one (1%) rated "high." The confidence assessments of the network meta-analysis estimates are in Table E3 (see Appendix E3).

Probabilistic analysis indicated that chlorpromazine IV/IM (SUCRA=87.3%) is most likely to be superior for adequate pain relief at 2 hours. The probabilistic analysis is listed in Table E4 (see Appendix E3, available at http://www.annemergmed.com), and its underlying cumulative rankograms are presented in Figure 4A. The complete trial data (raw) for adequate pain relief at 2 hours are in Appendix E5 (available at http://www.annemergmed.com).

Change in Pain Intensity at 1 Hour. There was evidence of statistically significant incoherence in the network at the overall level ($chi^2(9) = 45.84$, P=0.00) for change in pain intensity at 1 hour, so the results of network meta-analysis for this outcome will not be generalizable.

Need for Rescue Drug at 2 Hours. The network meta-analysis found with moderate to high certainty that 9 agents or combinations of agents in comparison with placebo are associated with decreased likelihood of need for rescue drug at 2 hours: metoclopramide IV-ibuprofen IV (OR 0.01, 95% CrI 0.00 to 0.38; high certainty), metoclopramide IV-dexketoprofen IV (OR 0.04, 95% CrI 0.00 to 0.44; high certainty), chlorpromazine IV/IM (OR 0.11, 95% CrI 0.06 to 0.22; moderate certainty), prochlorperazine IV/IM (OR 0.15, 95% CrI 0.07 to 0.30; moderate certainty), metoclopramide IV-dexamethasone IV (OR 0.15, 95% CrI 0.04 to 0.56; moderate certainty), lidocaine IV (OR 0.25, 95% CrI 0.09 to 0.71; moderate certainty), metoclopramide IV-lidocaine intranasal (OR 0.25, 95% CrI 0.08 to 0.81; moderate certainty), metoclopramide IV/IM (OR 0.25, 95% CrI 0.15 to 0.40; moderate certainty), and dexketoprofen IV (OR 0.27, 95% CrI 0.13 to 0.60; moderate certainty). The network meta-analysis estimates of all pairwise comparisons are in Table E5 (see Appendix E3). The summary of the risk of bias is illustrated in Figure 3B. There was no evidence of incoherence at the overall level (Table E5, [see Appendix E3]) or among any of the pairwise comparisons (Figure E4 [see Appendix E4]). Confidence in the effect estimates was

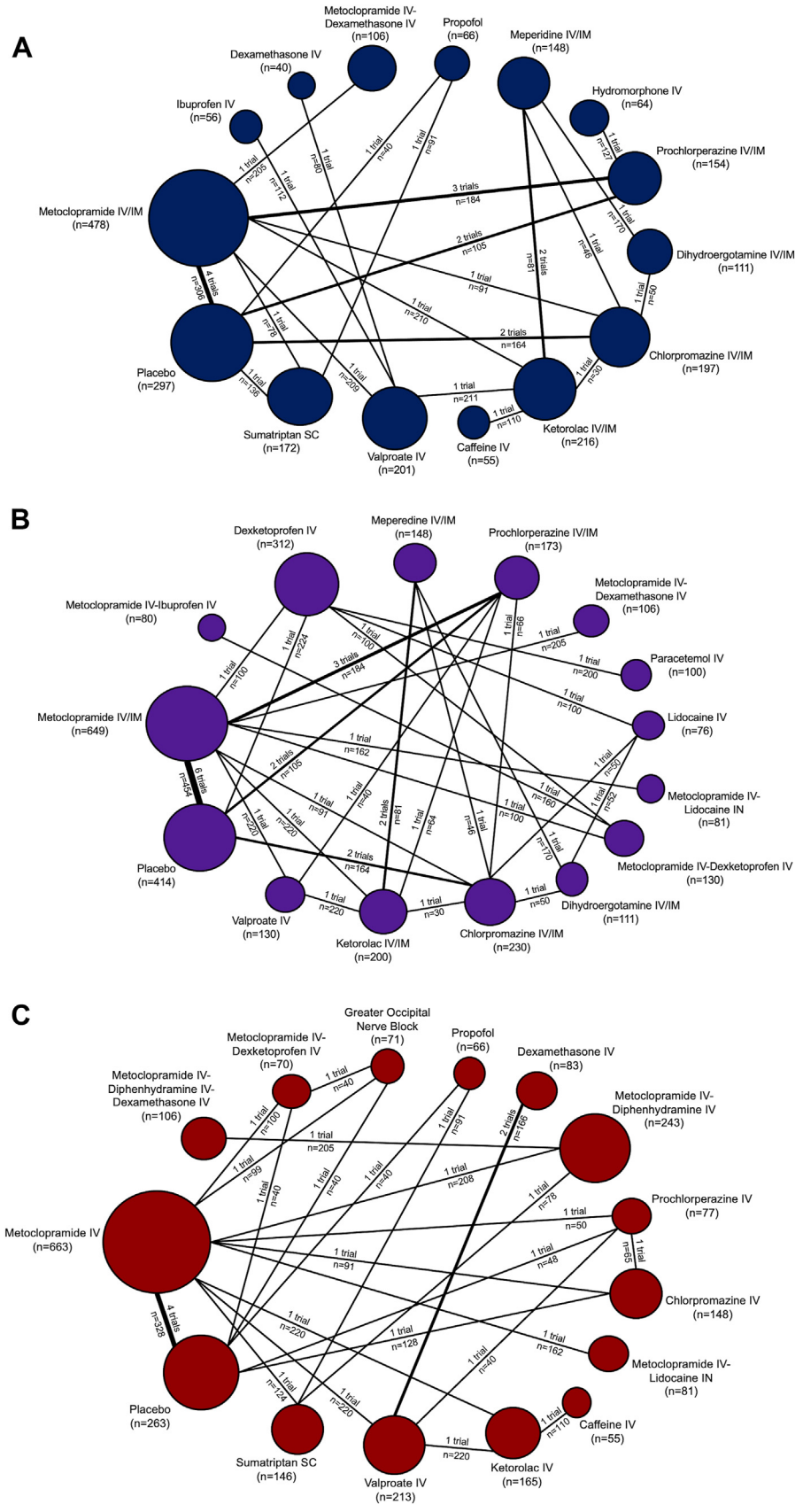

Figure 2. *A,* Network configuration of pharmacologic therapies for the outcome of adequate pain relief at 2 hours (24 trials; n=2,361). The area of the circles is based on the total number of participants assigned to each therapy among all trials included in

variable: 63 estimates (60%) rated "very low," 15 (14%) rated "low," 19 (18%) rated "moderate," and 8 (8%) rated "high." The confidence assessments of the network meta-analysis estimates are in Table E6 (see Appendix E3, available at http://www.annemergmed.com).

Probabilistic analysis indicated that chlorpromazine IV/IM (SUCRA=93.2%) is most likely to be superior for need for rescue drug (not needing rescue drug) at 2 hours. The probabilistic analysis is listed in Table E7 (see Appendix E3, available at http://www.annemergmed.com), and its underlying cumulative rankograms are presented in Figure 4B. The complete trial data (raw) for need for rescue drug at 2 hours are in Appendix E5.

Significant Adverse Reaction. The network meta-analysis found with moderate certainty that 2 drugs in comparison with placebo are associated with increased likelihood of significant adverse reaction: propofol (OR 11.11, 95% CrI 1.25 to 100.00) and chlorpromazine IV (OR 4.17, 95% CrI 1.64 to 12.50). The network meta-analysis estimates of all pairwise comparisons are in Table E8 (see Appendix E3, available at http://www.annemergmed.com). The summary of the risk of bias is illustrated in Figure 3C. There was no evidence of incoherence at the overall level (Table E8, [see Appendix E3]) or among any of the pairwise comparisons (Figure E6 [see Appendix E4]) http://www.annemergmed.com. Confidence in the effect estimates was variable: 74 estimates (70%) rated "very low," 26 (25%) rated "low," 5 (5%) rated "moderate," and none (0%) rated "high." The confidence assessments of the network meta-analysis estimates are in Table E9 (see Appendix E3, available at http://www.annemergmed.com).

Probabilistic analysis indicated that dexamethasone IV (SUCRA=79.5%) is most likely to be superior for the outcome of significant adverse reaction (not causing adverse reaction). The probabilistic analysis is listed in Table E10 (see Appendix E3, available at http://www.annemergmed.com), and its underlying cumulative rankograms are presented in Figure 4C. The complete trial data (raw) for significant adverse reactions are in Appendix E5.

LIMITATIONS

Our systematic review and network meta-analysis have limitations. First, we included only English language studies; however, language restriction in systematic reviews and meta-analyses in medicine has not been shown to result in systematic bias or significantly impact effect estimates.[93,94] Second, we assumed that an intravenous crystalloid bolus does not influence effectiveness. Reduced oral intake may be a migraine precipitant, and an intravenous crystalloid bolus could have reduced pain intensity in clinically dehydrated participants.[95] Seven studies infused an intravenous crystalloid bolus (5 mL/kg or 500 to 1000 mL) as a component of the study interventions, and network meta-analysis of data from hypovolemic participants could potentially inflate the effect estimates for those interventions with regards to the effectiveness outcomes.[38,41,65,75,78,86,89] Third, the transitivity assumption may be challenged by clinical heterogeneity in proportion of male subjects and migraine type and conceptual heterogeneity in inclusion criteria (eg, diagnostic criteria, pain intensity), exclusion criteria, definition of outcomes (eg, adequate pain relief), and individual drug regimen. The trials that enrolled only participants with a prespecified, moderate to severe pain intensity contributed data that comprised at least 20% of a number of the nodes within the effectiveness networks.[21,31,39,59-61,63,69,72,73,75,83] Consequentially, the network meta-analysis may have significantly deflated the effect estimates of hydromorphone IV, dexamethasone IV, sumatriptan subcutaneous (SC), placebo, prochlorperazine IV/IM, chlorpromazine IV/IM, propofol, and valproate IV for the outcome of adequate pain relief. Similarly, the network meta-analysis may have significantly deflated the effect estimates of metoclopramide IV-ibuprofen IV, metoclopramide IV-dexketoprofen IV, placebo, dexketoprofen IV, and chlorpromazine IV/IM for the outcome of need for rescue drug. Five different pain scales were used, but the descriptions of adequate pain relief defined in each trial were clinically equivalent, if not identical. The metoclopramide node is an example of an intervention in the network that was comprised of varying drug dosing regimens of the same agent. Although the metoclopramide dose does not seem to affect pain relief and incidence of side effects, the administration rate may be influential.[96] Three out of the 9 metoclopramide IV/IM arms in the network for adequate pain relief involved intravenous infusions, and the remaining arms involved

the network. The thickness of the lines is based on the total number of studies directly comparing the two therapies. Metoclopramide IV/IM is the most connected (most direct comparisons) and largest node (greatest pooled sample size), so its effect estimates would be expected to be least subject to bias and most reliable. Dexamethasone IV is the least connected and one of the smallest nodes, so its effect estimates would be expected to be most prone to bias and least reliable. *B,* Network configuration of pharmacologic therapies for the outcome of need for rescue drug at 2 hours (27 trials; n=2,942). *C,* Network configuration of pharmacologic therapies for the outcome of significant adverse reaction (22 trials; n=2,450). *IM,* intramuscular; *IN*, intranasal; *IV*, intravenous; *SC*, subcutaneous.

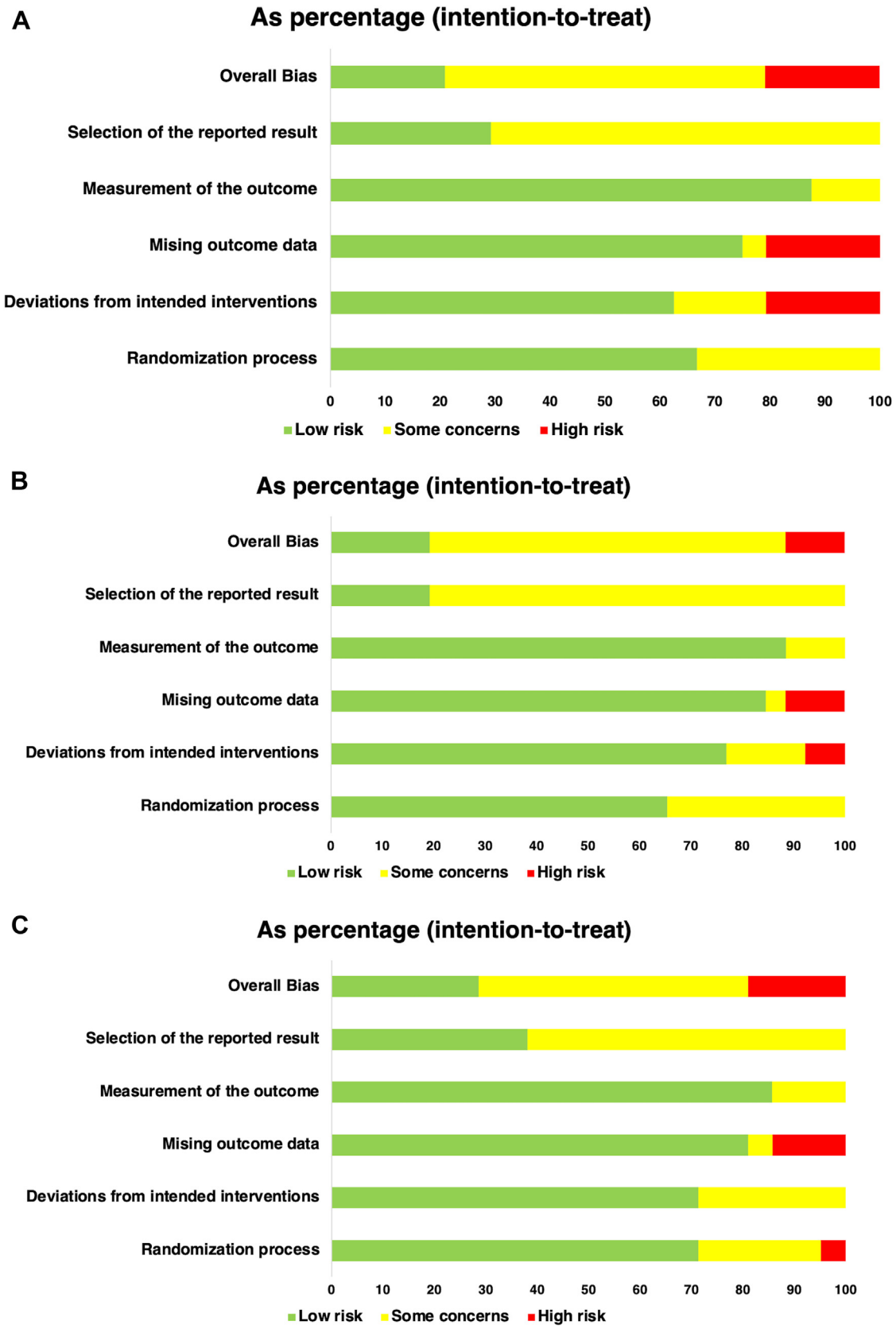

Figure 3. *A,* Summary of the risk of bias across the studies included in network meta-analysis for the outcome of adequate pain relief at 2 hours. *B,* Summary of the risk of bias across the studies included in network meta-analysis for the outcome of need for rescue drug at 2 hours. *C,* Summary of the risk of bias across the studies included in network meta-analysis for the outcome of significant adverse reaction.

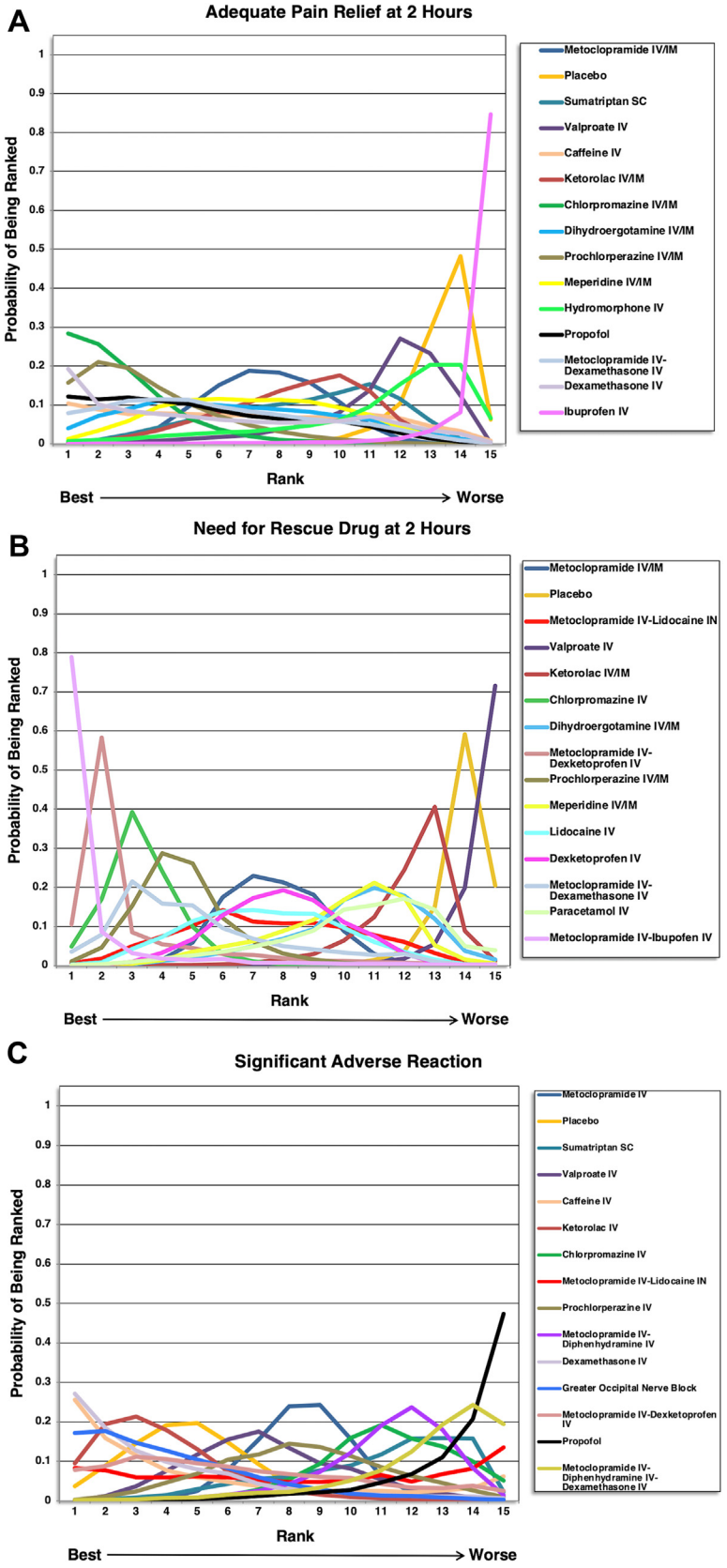

Figure 4. *A,* Cumulative rankograms of pharmacologic therapies for the outcome of adequate pain relief at 2 hours. A cumulative rankogram presents on the vertical axis the probability for the intervention to assume each of the possible ranks that are presented

Table 1. Final classification of 15 interventions based on network meta-analysis of migraine therapies for the outcome: Adequate pain relief at 2 hours.

Certainty of the Evidence and Classification* of Intervention	Intervention†	Intervention vs Reference (OR [95% CrI])	SUCRA
High certainty (moderate to high certainty evidence)‡			
Definitely among the most effective	—	—	—
Possibly among the most effective	—	—	—
Possibly among the least effective	—	—	—
Definitely among the least effective	Placebo (M)	0.26 (0.13-0.51)	0.1184
	Ibuprofen IV (M)	0.07 (0.01-0.57)	0.0247
Low certainty (low to very low-certainty evidence)‡			
Uncertain – likely among the most effective	—	—	—
Uncertain – possibly among the most effective	Chlorpromazine IV/IM (VL)	2.50 (0.91-6.11)	0.8751
	Prochlorperazine IV/IM (VL)	2.03 (0.81-5.29)	0.8099
	Propofol (VL)	1.49 (0.34-6.82)	0.6854
	Dexamethasone IV (L)	1.42 (0.16-14.42)	0.6521
	Metoclopramide IV-Dexamethasone IV (VL)	1.35 (0.33-5.55)	0.6479
	Dihydroergotamine IV/IM (VL)	1.18 (0.25-5.16)	0.5986
	Caffeine IV (L)	1.15 (0.15-9.01)	0.5877
Uncertain – possibly among the least effective	Meperidine IV/IM (VL)	1.06 (0.27-3.84)	0.5569
	Reference (Metoclopramide IV/IM)	—	0.5322
	Ketorolac IV/IM (L)	0.83 (0.27-2.70)	0.4609
	Sumatriptan SC (VL)	0.78 (0.24-2.33)	0.4360
	Hydromorphone IV (VL)	0.40 (0.07-2.44)	0.2610
	Valproate IV (L)	0.44 (0.12-1.72)	0.2533
Uncertain – likely among the least effective	—	—	—

CrI, credible interval; *IM,* intramuscular; *IV,* intravenous; *OR,* odds ratio; *SC,* subcutaneous; *SUCRA,* Surface under the cumulative ranking curve.
*Categories do not inform value judgments about the importance of the effects.
†Letters in brackets represent the certainty of evidence for each intervention when compared with the reference (metoclopramide IV/IM): *H,* high; *M,* moderate; *L*, low; *VL,* very low.
‡The certainty of evidence for the pairwise comparison was determined by the confidence rating of the corresponding network meta-analysis estimate.

bolus or intramuscular injections. On the other hand, the incidence of drug-induced akathisia is probably not influenced by the intravenous infusion rates of the dopamine D2 receptor antagonists, metoclopramide and prochlorperazine.[97-99] In the network for adequate pain relief, the chlorpromazine dose varied from 0.1 mg/kg to 1 mg/kg, whereas the prochlorperazine dose was consistent (10 mg). Sparsity of the networks, that is, a single study or no sources of direct evidence for many pairwise comparisons, will limit investigation of the influence of potential effect modifiers and the evaluation of transitivity. Despite the clinical and conceptual heterogeneity, there was no incoherence detected among any of the pairwise comparisons within the presented networks. Fourth, the adverse reactions in the composite safety outcome vary in clinical importance; for example, hypotension may be considered more significant than akathisia. However, only 13 included studies (892 participants) can provide data for hypotension as an independent outcome, and this would generate a very sparse network whose analysis would not be likely to provide meaningful results. Because we did not extract adverse reactions that are specific to sumatriptan (eg, chest tightness, palpitations, flushing), our network meta-analysis may have failed to identify a relatively less favorable safety profile for sumatriptan.[100] Nonetheless, significant adverse reactions appear to be rare, and the safety profile differences between the pharmacologic therapies may not be clinically important. Fifth, nonstandardized reporting across the included studies probably underestimates the adverse reaction rates within

on the horizontal axis. For example, chlorpromazine IV/IM has 28% probability of being #1 (ranked first), and ibuprofen IV has an 85% probability of being #15 (ranked last). This ranking of the interventions is uncertain as the majority are represented by rankograms with similar distributions and overlap of probabilities across the ranks. *B,* Cumulative rankograms of pharmacologic therapies for the outcome of need for rescue drug at 2 hours. *C,* Cumulative rankograms of pharmacologic therapies for the outcome of significant adverse reaction. *IM,* intramuscular; *IN*, intranasal; *IV*, intravenous; *SC*, subcutaneous.

Table 2. Final classification of 15 interventions based on network meta-analysis of migraine therapies for the outcome: Need for rescue drug at 2 hours.

Certainty of the Evidence, and Classification*of Intervention	Intervention†	Intervention vs Reference (OR [95% CrI])	SUCRA
High certainty (moderate to high certainty evidence)‡			
Definitely among the most effective	Chlorpromazine IV/IM (M)	0.44 (0.23-0.87)	0.8330
Possibly among the most effective	—	—	—
Possibly among the least effective	Ketorolac IV/IM (M)	2.38 (1.10-5.26)	0.3234
Definitely among the least effective	Placebo (M)	4.00 (2.50-6.67)	0.2048
	Valproate IV (H)	5.26 (2.44-12.50)	0.0769
Low certainty (low to very low-certainty evidence)‡			
Uncertain – likely among the most effective	—	—	—
Uncertain – possibly among the most effective	Metoclopramide IV-Ibuprofen IV (L)	0.05 (0.00-1.54)	0.9461
	Metoclopramide IV-Dexketoprofen IV (L)	0.22 (0.01-1.76)	0.8553
	Prochlorperazine IV/IM (VL)	0.60 (0.31-1.16)	0.7366
	Metoclopramide IV-Dexamethasone IV (VL)	0.61 (0.18-1.98)	0.6987
Uncertain – possibly among the least effective	Lidocaine IV (VL)	0.97 (0.36-2.96)	0.5416
	Metoclopramide IV-Lidocaine IN (VL)	0.99 (0.35-2.93)	0.5272
	Reference (Metoclopramide IV/IM)	—	0.5250
	Dexketoprofen IV (VL)	1.06 (0.48-2.56)	0.5033
	Meperidine IV/IM (VL)	1.52 (0.57-4.17)	0.3706
	Dihydroergotamine IV/IM (VL)	1.67 (0.57-5.26)	0.3603
	Paracetamol IV (VL)	1.67 (0.48-6.67)	0.3273
Uncertain – likely among the least effective	—	—	—

CrI, credible interval; *IM*, intramuscular; *IN*, intranasal; *IV*, intravenous; *OR*, odds ratio; *SUCRA*, Surface under the cumulative ranking curve.
*Categories do not inform value judgments about the importance of the effects.
†Letters in brackets represent the certainty of evidence for each intervention when compared with the reference (metoclopramide IV/IM): H, high; M, moderate; L, low; VL, very low.
‡The certainty of evidence for the pairwise comparison was determined by the confidence rating of the corresponding network meta-analysis estimate.

the network. In addition, we imputed "no event" or "zero" for participants with missing data for analysis by assignment-to-intervention, and this may have deflated the network meta-analysis estimates for all outcomes; however, only 0.8% (adequate pain relief), 1.1% (need for rescue drug), and 2.1% (significant adverse reaction) of participants were represented by imputed data within the networks. Sixth, small sample sizes or small number of studies per pairwise comparison may mask potentially important heterogeneity between studies, and this may be reflected in the overlap of wide CrIs of treatment effects estimated by individual studies. The imbalance in the evidence contributing to each pharmacologic therapy node will limit the power and reliability of the overall analysis.[101,102] Largely due to study limitations and imprecision, there remains uncertainty in the relative effectiveness and safety of many of the pharmacologic therapies.

DISCUSSION

We performed a systematic review and network meta-analysis to identify the relatively more effective and safer pharmacologic therapies for migraine in adult patients who present to the ED. Our network meta-analysis found that chlorpromazine IV/IM and metoclopramide IV-ibuprofen IV each are most likely to be superior for 1 of 2 measures of effectiveness, and dexamethasone IV is most likely to be superior for safety. However, these therapies have primarily low- to very low-certainty evidence underlying their comparisons with the other therapies. In this situation, focusing solely on the probabilistic analysis can misdirect network meta-analysis interpretation.[103] Interpretation of network meta-analysis will also be complex when the network includes a large number of interventions and, consequently, a large number of pairwise comparisons.[103] To more accurately classify interventions in categories from among the best to among the worst according to the magnitude of effects and evidence certainty, we applied a modified grading of recommendations assessment, development, and evaluation (GRADE) approach using a minimally contextualized framework and GRADE guidelines 26 to draw conclusions (Tables 1-3) from our network meta-analysis results ("Additional Details of the Modified GRADE Approach Using a Minimally Contextualized Framework" is in Appendix E2).[103-106] In summary, ibuprofen IV is *definitely* among the least

Table 3. Final classification of 15 interventions based on network meta-analysis of migraine therapies for the outcome: Significant adverse reaction.

Certainty of the Evidence and Classification* of Intervention	Intervention†	Intervention vs Reference (OR (95% CrI))	SUCRA
High certainty (moderate to high certainty evidence)‡			
Definitely among the least harmful	—	—	—
Possibly among the least harmful	—	—	—
Possibly among the most harmful	—	—	—
Definitely among the most harmful	—	—	—
Low certainty (low to very low-certainty evidence)‡			
Uncertain – likely among the least harmful	—	—	—
Uncertain – possibly among the least harmful	Dexamethasone IV (VL)	0.23 (0.01-2.80)	0.7951
	Ketorolac IV (L)	0.29 (0.05-1.33)	0.7937
	Greater Occipital Nerve Block (VL)	0.29 (0.03-2.05)	0.7708
	Placebo (VL)	0.41 (0.14-1.43)	0.7249
	Caffeine IV (L)	0.26 (0.00-15.85)	0.7099
	Metoclopramide IV-Dexketoprofen IV (VL)	0.54 (0.05-5.21)	0.6138
	Valproate IV (L)	0.75 (0.18-2.61)	0.5492
Uncertain – possibly among the most harmful	Prochlorperazine IV (VL)	0.98 (0.26-3.93)	0.4716
	Metoclopramide IV-Lidocaine IN (VL)	1.00 (0.03-33.33)	0.4726
	Reference (Metoclopramide IV)	—	0.4691
	Chlorpromazine IV (VL)	1.79 (0.63-5.88)	0.2731
	Sumatriptan SC (VL)	1.85 (0.37-10.00)	0.3013
	Metoclopramide IV-Diphenhydramine IV (L)	1.92 (0.63-5.56)	0.2700
	Metoclopramide IV-Diphenhydramine IV-Dexamethasone IV (VL)	2.86 (0.53-16.67)	0.1792
	Propofol (VL)	4.76 (0.68-33.33)	0.1058
Uncertain – likely among the most harmful	—	—	—

CrI, credible interval; *IM*, intramuscular; *IN*, intranasal; *IV*, intravenous; *OR*, odds ratio; *SC*, subcutaneous; *SUCRA*, Surface under the cumulative ranking curve.
*Categories do not inform value judgments about the importance of the effects.
†Letters in brackets represent the certainty of evidence for each intervention when compared with the reference (metoclopramide IV): H, high; M, moderate; L, low; VL, very low.
‡The certainty of evidence for the pairwise comparison was determined by the confidence rating of the corresponding network meta-analysis estimate.

effective for adequate pain relief. With regards to need for rescue drug, chlorpromazine IV/IM is *definitely* among the most effective, whereas valproate IV is *definitely,* and ketorolac IV/IM is *possibly* among the least effective. The relative safety of the pharmacologic therapies cannot be determined.

Our network meta-analysis results are variably consistent with the most recent guidelines.[5,107] The 2016 American Headache Society Evidence Assessment, citing 25 (39%) of the randomized controlled trials we identified in our systematic review, recommends that clinicians "should offer" metoclopramide IV, prochlorperazine IV, and sumatriptan SC and "may offer" parenteral chlorpromazine.[5] The 2015 Canadian Headache Society Systematic Review and Recommendations, citing 24 (38%) of our included randomized controlled trials, "strongly" recommend prochlorperazine IV, metoclopramide IV, sumatriptan SC, lysine acetylsalicylic acid IV, and ketorolac IV/IM and "weakly" recommend chlorpromazine IV.[107]

These guideline recommendations are supported by our network meta-analysis, which found that chlorpromazine IV/IM, prochlorperazine IV/IM, and metoclopramide IV/IM are all *probably* more effective than placebo for pain relief as single agents without the need for rescue drug.[5,107] Further, we can conclude that chlorpromazine IV/IM is *definitely* and prochlorperazine IV/IM is possibly (uncertain evidence) among the most effective for pain relief as single agents. The American and Canadian Headache Societies justify their weaker recommendation for chlorpromazine IV, citing an association with unpleasant side effects.[5,107] Our network meta-analysis finding that chlorpromazine IV is *probably* more likely than placebo to be associated with significant adverse reaction and possibly (uncertain evidence) among the least safe agents supports its weak recommendation by the American and Canadian Headache Societies.[5,107] Considering our network meta-analysis results for chlorpromazine IV/IM's effectiveness and chlorpromazine IV's safety, a reasonable clinical approach

may be to administer chlorpromazine IM instead of IV to maintain effectiveness while potentially minimizing the likelihood of adverse reaction. Our network meta-analysis findings conflict with the strong recommendation of ketorolac IV/IM by the Canadian Headache Society as we can conclude that ketorolac is *possibly* among the least effective as a single agent and possibly (uncertain evidence) among the least effective for adequate pain relief.[107] Our network meta-analysis did not find evidence with sufficient certainty to support the strong guideline recommendations for sumatriptan SC or lysine acetylsalicylic acid IV.[5,107] When considering the most recent guidelines, our systematic review and network meta-analysis of a greater number of randomized controlled trials in only ED populations may inform the development of more contemporary guideline recommendations for migraine therapy in the ED.[5,107]

Interestingly, the American and Canadian Headache Societies disagree about the use of valproate IV.[5,107] The American Headache Society suggests that valproate IV "may be offered," and the Canadian Headache Society recommends against its use.[5,107] Our conclusions that valproate IV is *definitely* among the least effective as a single agent and possibly (uncertain evidence) among the least effective for pain relief is consistent with Canadian Headache Society but not American Headache Society guidelines.[5,107] Parenteral antihistamines are often given as a 2-drug combination with dopamine D2 receptor antagonists to try to reduce the incidence of akathisia, and the Canadian Headache Society specifically mentions that clinicians can consider coadministration of diphenhydramine with prochlorperazine to prevent extrapyramidal side effects.[1,107,108] However, we can conclude that the drug combinations metoclopramide IV-diphenhydramine IV and metoclopramide IV-diphenhydramine IV-dexamethasone IV are possibly (uncertain evidence) among the least safe therapies. The unfavorable network meta-analysis results for safety of drug combinations that included diphenhydramine IV appear to be driven by an association with sedation, a finding that has also been reported by another meta-analysis.[109]

The ongoing opioid overdose epidemic has been well documented. Although opioid use for treatment of migraine in EDs across the United States has declined 10% annually from 2010 to 2017, it remains as high as 28%.[1,7] The American Headache Society advises that hydromorphone IV "may be avoided," and the Canadian Headache Society recommends against the use of morphine IV and tramadol IM.[5,107] The 2013 American Academy of Neurology's Top 5 Recommendations in the Choosing Wisely campaign urges clinicians to avoid using an opioid "except as a last resort," and the American College of Emergency Physicians recommends "preferentially using nonopioid medications in the treatment of acute primary headaches in ED patients."[110,111] As it pertains to effectiveness, our conclusions that meperidine IV/IM and hydromorphone IV are possibly (uncertain evidence) among the least effective for pain relief support guideline recommendations to preferentially use nonopioid analgesics for treatment of migraine in the ED.[5,107,110,111]

In conclusion, according to Bayesian network meta-analysis of pharmacologic therapies for migraine in adult patients presenting to the ED, ibuprofen IV is definitely among the least effective for adequate pain relief. Chlorpromazine IV/IM is definitely among the most effective, valproate IV is definitely among the least effective, and ketorolac IV/IM is possibly among the least effective as single agents obviating the need for rescue drug. The relative safety of the pharmacologic therapies cannot be determined with sufficient certainty. Further, randomized controlled trials of parenterally administered, and perhaps more relatively effective pharmacologic therapies such as chlorpromazine, prochlorperazine, and metoclopramide-NSAID combinations should more robustly establish which are the best options for migraine in the ED.

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