Evidence-based Practice Center Systematic Review Protocol

Project Title: Acute Migraine Treatment in Emergency Settings

I. Background and Objectives for the Systematic Review

Migraine is a neurovascular disorder characterized by dysfunction of the central and peripheral nervous systems and intracranial vasculature.[1] Acute exacerbations of episodic and chronic migraine cause severe and disabling pain that often results in visits to an emergency department (ED) and decreased productivity and missed time from work, school, and other activities.[2] In the United States, migraine and related medical issues result in costs of more than $13 billion per year due to lost productivity. In Canada, this cost has been estimated at $3,025/patient due to medical and indirect costs.[3]

Migraine has a negative impact on overall quality of life.[4] It is associated with psychiatric and medical comorbidities including major depressive disorder, bipolar disorder, anxiety and social phobias, cardiovascular risk,[5] and stroke.[6] Inadequate care of migraine is common: only 56 percent of migraine patients have been diagnosed correctly, and 49 percent use only over-the-counter rather than prescription medications to treat their headache.[7]

Acute Exacerbations and Emergency Department Presentation

Migraine causes acute headaches, which typically last 4 hours to 3 days if untreated and which frequently require bed rest, pain medications, and time off from work and other activities. Although most patients with migraine function normally between attacks, for many, migraine is a pervasive disorder that interferes with work, family, and social life.[1] Most individuals with migraine are able to treat their attacks at home, but this treatment is not always successful. Furthermore, when the initial oral acute treatment fails, subsequent attempts are likely to fail as well. Of Americans with migraine, 7 percent reported using an ED or urgent care center for treatment of severe headache within the previous 12 months.[8] In a representative sample of adult ED visits in the United States, headaches accounted for 2.2 percent of visits or 2.1 million ED visits per year.[9] In fact, a 5-month study in an American health maintenance organization found that migraine sufferers accounted for more ambulatory ED visits than patients with asthma (1.9 vs. 1.0 percent).[10] In addition, migraine sufferers were more often found to have multiple ED visits.[11]

While headache is a common cause of presentation to the ED, there is substantial practice variability among emergency clinicians in both the United States and Canada.[12-15] Twenty disparate parenteral agents are used in U.S. EDs to treat acute migraine.[12] There is substantial variability across EDs. For example, dopamine antagonists are used in 60 percent of visits in some EDs when compared with only 20 percent of visits in others.[14]

Acute Migraine Management

Acute headache pain and symptoms

Many agents are used to treat acute migraine, including 5-hydroxytryptamine (HT) receptor agonists (e.g., triptans), dopamine receptor antagonists (e.g., phenothiazines, metoclopramide),

ergot derivatives (e.g., dihydroergotamine), intravenous nonsteroidal anti-inflammatory agents, and opioids. A variety of selective 5-HT_1 receptor agonists have been developed and represent a class of drugs called triptans. These agents are indicated for the acute treatment of migraine in adults; however, reduced efficacy with delayed administration,[16] the need for cardiac risk stratification prior to administration,[17] and frequent adverse events[18] limit their use in many EDs. Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and headache relapse.[11] The first objective of this comparative effectiveness review (CER) is to assess the effectiveness of various parenteral medications for adult patients with acute migraine who come to an ED for treatment.

Side effects

The second objective of this CER is to assess important immediate and longer term side effects of the different interventions. For example, opioids may be associated with drowsiness and impaired ability to function. In addition, both metoclopramide and the phenothiazines are considered to be equally efficacious, yet both agents have important immediate and subacute side effects. This CER will specifically examine the efficacy of metoclopramide and the phenothiazines and investigate their side effects, particularly akathisia and extrapyramidal events.

Prevention of Recurrence

Some patients with status migrainosus suffer a short-term recurrence that results in a return visit to a physician or ED. Research has shown that short-term or single-dose systemic corticosteroids (CSs), delivered intravenously (e.g., dexamethasone), prevent headache recurrence after treatment in an ED for acute migraine.[19] However, they are infrequently used and have important short- and long-term side effects.[19] A third focus of this review will be to examine the benefit and risk of using CSs for preventing recurrence of acute migraine.

Review Rationale

The research used to support current guidelines for treatment of acute migraine is dated, not adequately synthesized, insufficient, and continues to add to clinical uncertainty, resulting in wide variation of practice. Various important management trials of acute migraine headache have been completed in the past decade. The purpose of conducting this CER is to synthesize the current evidence in areas where reviews are lacking and to update reviews in areas where the data have been previously synthesized. The resulting report will provide the depth of understanding needed to inform management and policy decisions and hopefully improve migraine headache care provided in the ED.

II. The Key Questions

The Key Questions (KQs) were posted on the Agency for Healthcare Research and Quality (AHRQ) Effective Health Care Program Web site for public comment. Following review of the comments and discussion with the Key Informants, AHRQ, and the Eisenberg Center, no

changes were made to the original KQs; however, the following comments were incorporated into the background material or inclusion criteria, as appropriate:

- The importance of distinguishing between recurrent headache and recurrent visits to the ED.
- The consideration of combinations of treatments.
- Addressing sedation as an adverse event.
- The followup period for longer term outcome studies.
- Whether or not there will be sufficient information reported on subgroups to warrant their inclusion.

The KQs to be addressed by this CER are:

Question 1

What is the comparative effectiveness of parenteral pharmacological interventions versus standard care, placebo, or an active treatment in the treatment of acute migraine headaches in adults visiting the ED?

Question 2

What is the comparative effectiveness of adding parenteral or oral CSs versus adding placebo to acute parenteral pharmacological interventions to prevent recurrence of acute migraine headaches in adults after being treated in the ED?

Question 3

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

Question 4

Does the development of adverse events (especially akathisia) differ following the administration of anticholinergic agents and phenothiazines when compared with anticholinergic agents and metoclopramide?

Question 5

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

Question 6

Does the effectiveness and safety of adding parenteral or oral CSs to acute parenteral pharmacological interventions vary in different subgroups, including sex, race, duration of headaches, and nonresponders?

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The PICOTS framework is the same for each KQ and will guide the all stages of the systematic review, including literature searching, study selection, and data extraction.

- **Population(s) (KQs 1–6)**

  - Adult patients (≥ 18 years) with severe acute migraine headache presenting to an ED or equivalent setting and receiving parenteral therapy.
  - We will consider the following subgroups: sex, race, duration of headaches, and non-responders.
  - To address KQ 4, we will specifically look at the subgroup of patients who are taking anticholinergics plus either parenteral phenothiazines or parenteral metoclopramide.

- **Interventions**

  - **In-ED treatment (KQs 1, 3, 4, and 5)**

    First-line parenteral (intravenous/intramuscular/subcutaneous) interventions:

    - Metoclopramide (Maxeran/Reglan)
    - Dihydroergotamine (DHE)
    - NSAIDs (ketorolac [Toradol])
    - Phenothiazines (chlorpromazine [Largactil], prochlorperazine [Stematil], droperidol)
    - Magnesium sulfate ($MgSO_4$)
    - Triptan agents
    - Meperidine (Demerol)
    - Valproic acid
    - Other agents: propafol (Diprivan), ketamine (Ketalar), opioids

  - **Prevention of relapse (KQs 2 and 6)**

    - Parenteral corticosteroids (dexamethasone, others)
    - Oral CSs (prednisone, others)
      (Note: CSs must be used in addition to one of the parenteral interventions listed above.)

  See Appendix A for a detailed table showing generic and trade names, usual dose, frequency, and mode of administration of pharmacological interventions of interest that have been approved by the U.S. Food and Drug Administration.

- **Comparators**

  - **In-ED treatment (KQs 1, 3, 4, and 5)**

    We are interested in all comparators, including standard care, placebo, or an active comparator. We will consider any route of administration (i.e., parenteral, oral, intranasal, sublingual). "Standard care" for migraine has changed over time. For example, many of

the earlier trials compared an opioid or placebo with the active treatment arm. More recent trials have employed variable active comparators (e.g., DHE, metoclopramide, phenothiazines, ketorolac).

- **Prevention of relapse (KQs 2 and 6)**

  Standard parenteral therapy (i.e., one of the interventions listed above) plus placebo or no treatment.

- **Outcome measures:**

1. Pain relief/change in pain score (measured either as Visual Analog Scale [VAS] score, a Likert scale of pain, or a 10-point verbal scale)
2. Complete elimination of pain prior to ED discharge
3. Vital signs (i.e., blood pressure, pulse) in ED
4. Time in the ED (in minutes of total time and post-ED physician time)
5. Recurrence of headache (headache relieved in the ED and recurring within the followup period)
6. Health services utilization (e.g., return visit to ED defined as an unscheduled visit for worsening symptoms)
7. Quality of life/return to regular activities
8. Patient satisfaction with experience

- **Adverse effects of intervention(s)**

a. Sedation/somnolence
b. Dizziness
c. Restless legs/akathisia
d. Anxiety
e. Vomiting
f. Chest symptoms; palpitations
g. Skin flushing
h. Other side effects

- **Timing**

1. Pain assessment at presentation
2. Pain assessment at discharge (usually less than 6 hours) and up to 7 days postdischarge
3. Relapse of headache within 24–48 hours and recurrence of headache up to 7 days postdischarge
4. Adverse effects up to 3 months postintervention

- **Settings**

An ED or an equivalent setting (such as acute headache clinics and urgent care clinics seeing

patients with severe migraine headaches).

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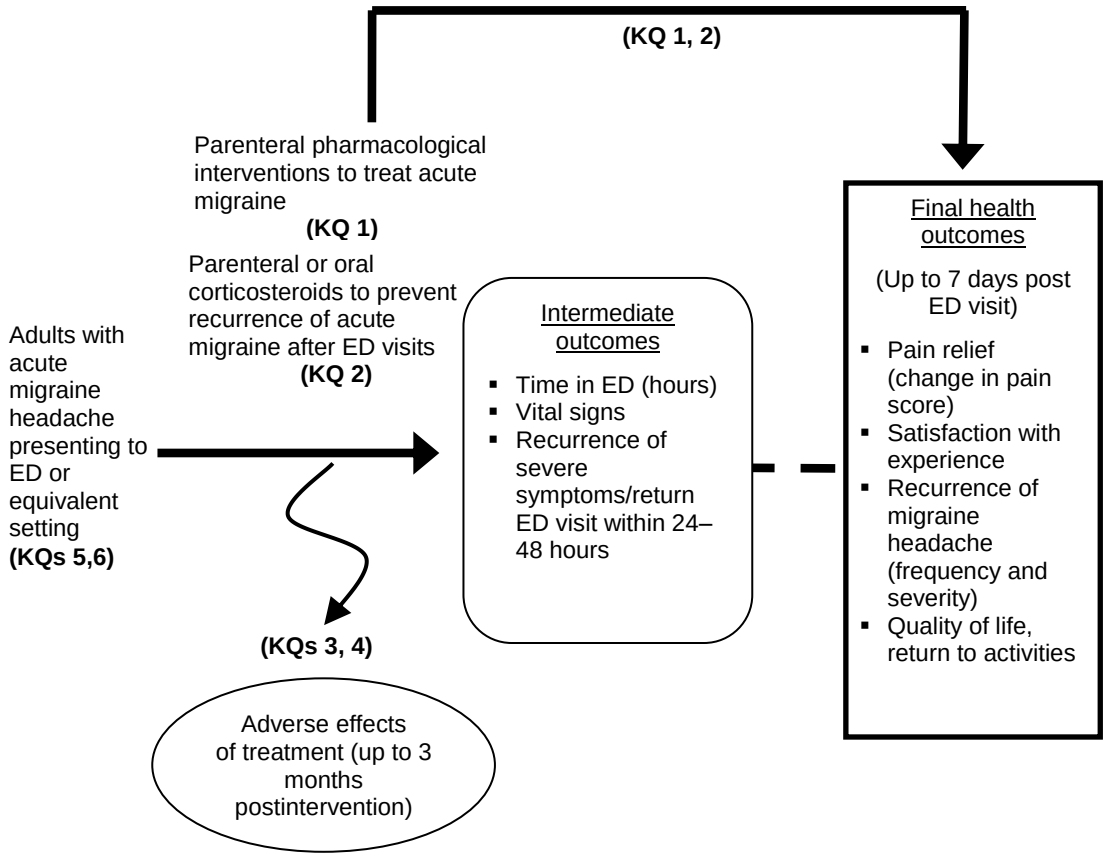
III. Analytic Framework

Figure 1: Analytic Framework



KQ = Key Question; ED = emergency department.

Figure 1 provides an analytic framework to illustrate the population, interventions, and outcomes that will guide the literature search and synthesis. This figure depicts the Key Questions within the context of the PICOTS described in the previous section. In general, the figure illustrates how parenteral pharmacological interventions and parenteral or oral corticosteroid interventions versus standard care, placebo, or an active comparator may result in intermediate outcomes such as time in ED, recurrence of severe symptoms, or return ED visits within 24–48 hours and in final outcomes such as pain relief, satisfaction with experience, quality of life, and return to activities. Adverse events may occur at any point after the treatment is received and will be assessed up to 3 months postintervention.

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IV. Methods

The methodological approaches that will be used for this review are described below.

A. Criteria for Inclusion/Exclusion of Studies in the Review

Table 1. Inclusion criteria

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

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ED = emergency department; NRCT = nonrandomized controlled trial; NSAIDs = nonsteroidal anti-inflammatory drugs; RCT = randomized controlled trial.

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Publication status and dates

Abstracts will be included if they provide sufficient outcome data. Authors will be contacted for additional data when clarification or additional information is required. There will be no date restrictions.

Language

There are no language restrictions. Non–English-language studies that meet our inclusion criteria will be translated.

Study selection

Two reviewers will independently screen the titles and abstracts (when available) of the search results using broad inclusion/exclusion criteria. Studies will be classified as "include", "exclude", or "unsure". The full text of studies classed as "include" or "unsure" will be retrieved for full review. Two reviewers will then independently review the full text of potentially relevant studies using a standard form that outlines the pre-determined inclusion and exclusion criteria. We will pre-test this form on a sample of studies. Disagreements will be resolved through consensus or third party adjudication, as needed.

B. Searching for the Evidence: Literature Search Strategies for Identification of Relevant Studies To Answer the Key Questions

The research librarian developed the search strategies in collaboration with the research team and the Technical Expert Panel. The search will be conducted first in MEDLINE, as this is the most comprehensive database, and will be replicated in EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effectiveness (DARE), CINAHL, International Pharmaceutical Abstracts, and PASCAL. Databases will be searched from inception. No search filters will be applied.

Appendix B presents the MEDLINE search strategy. The search terms will be adapted to accommodate the controlled vocabulary and search languages of each database.

We will hand search key conference proceedings in emergency medicine, pain, headache, neuropharmacology, and neurology from 2008 to 2011.

We will also search relevant gray literature sources. This search will include trial registries such as ClinicialTrials.gov, metaRegister of Controlled Trials, WHO International Clinical Trials Registry Platform, and CenterWatch. We will conduct a search of the U.S. Food and Drug Administration Web site to identify additional regulatory data. Further, the Web sites of pertinent associations such as the American Headache Society, the American Pain Society, and the Association of Emergency Physicians will be investigated. We will review the reference lists of included studies and relevant systematic reviews.

C. Data Abstraction and Data Management

Data will be extracted onto a standardized form and entered into a Microsoft Excel™ database (Microsoft Corp., Redmond, WA). Data will be extracted by one reviewer and checked for accuracy and completeness by another reviewer. Disagreements will be resolved through discussion or third-party adjudication, as needed. We will extract the following data: author identification, year of publication, source of study funding, study design characteristics and methodological quality criteria (see below), study population (including study inclusion and exclusion criteria, study withdrawals, length of study, duration of patient followup), patient baseline characteristics (age, sex, race, use of concurrent pharmacological interventions), details of the intervention and comparator (drugs used, dose, route of administration), and results for our outcomes of interest.

D. Assessment of Methodological Quality of Individual Studies

The Cochrane Collaboration Risk of Bias tool will be used to assess the internal validity of the randomized controlled trials and nonrandomized controlled trials.[20] The tool examines six domains (sequence generation, concealment of allocation, blinding of participants and personnel and outcome assessment, incomplete outcome data, selective outcome reporting, and "other" sources of data) and categorizes the overall risk of bias. Each separate domain is rated "yes," "unclear," or "no."

Blinding and incomplete outcome data will be assessed separately for subjective outcomes (e.g., quality of life or change in pain score) and objective outcomes (e.g., vital signs, time in ED). "Other sources of bias" will include stopping early for benefit and comparability of groups at baseline. The overall assessment is based on the responses to individual domains. If one or more individual domains are assessed as having a high risk of bias, the overall score will be rated as high risk of bias. The overall risk of bias will be considered low only if all components are rated as having a low risk of bias. The risk of bias for all other studies will be rated as unclear. In addition to assessing the risk of bias, we will record funding sources for each included study.

The Newcastle-Ottawa Scale will be used to assess cohort studies.[21] This scale includes eight items that assess sample selection, comparability of cohorts, and assessment of outcomes. If the item is adequately addressed in the study, one star will be allotted to that item, with the exception of the comparability of cohorts, which receives a maximum of two stars. The total number of stars is tallied with a maximum score of nine stars. In addition, information on funding sources will be collected as well.[22]

Decision rules regarding application of the tool will be developed a priori through discussions with content and methodology experts. A sample of studies will be used to pilot both tools. Two reviewers will independently assess the methodological quality of included studies. Discrepancies will be resolved through consensus or third-party adjudication, as needed.

E. Data Synthesis

The characteristics of included studies will be presented in evidence tables. The tables will include information on author, date of publication, study design, setting, treatment groups, inclusion/exclusion criteria, sample size, study quality, and outcomes with effect sizes. We will also develop tables that provide a summary of the evidence and a statement about the strength of evidence.

Mean differences will be calculated for continuous variables. Risk ratios and odds ratios will be calculated for dichotomous data. Results will be reported with accompanying 95 percent confidence intervals. If the studies are homogenous with respect to design, population, intervention, and outcomes, results will be pooled. Pooled risk ratios, odds rations, mean differences, or standardized mean difference with corresponding 95 percent confidence intervals will be calculated, as appropriate. We will use the random effects model for all meta-analyses with Review Manager 5.0 software (The Cochrane Collaboration, Copenhagen, Denmark).

The I^2 statistic will be used to measure heterogeneity. Reasons for heterogeneity will be explored through subgroup analyses and meta-regression (where there are at least 10 studies). Planned subgroup analyses include age, sex, race, duration of headaches, and nonresponders to treatment. Sensitivity analyses will be conducted to assess the robustness of the findings across study quality, publication status, study design (randomized controlled trials vs. nonrandomized controlled trials) and random effects versus fixed effects analyses.

For the key efficacy outcomes (e.g., complete elimination of pain in the ED, Visual Analog Scale score at discharge, and relapse after 48 hours), if feasible, we will conduct a mixed treatment analysis using a Bayesian network model to compare all interventions simultaneously and to use all available information on treatment effects in a single analysis.[23–25] Mean differences or log odds ratios will be modeled using noninformative prior distributions. Markov Chain Monte Carlo simulations will be performed using WinBUGS software (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom) to obtain simultaneous estimates of all interventions compared with placebo, as well as estimates of which interventions are the best.[26] A burn-in sample of 20,000 iterations, followed by 200,000 iterations, will be used to compute estimates. Results will be reported with 95 percent credibility intervals. All trial groups will be considered separately in the analysis.

Publication bias will be tested visually using the funnel plot, and quantitatively using the Begg[27] adjusted rank correlation test and Egger[28] regression asymmetry test.

F. Grading the Evidence for Each Key Question

We will evaluate the overall strength of the evidence for key ***efficacy*** (e.g., complete elimination of pain in the ED, Visual Analog Scale score at discharge, and relapse after 48 hours) and ***safety*** (e.g., sedation, dizziness, restless legs/akathisia, anxiety, and vomiting) outcomes using the Grade approach found in "Chapter 10. Grading the Strength of a Body of Evidence When Comparing Medical Interventions" of the AHRQ *Methods Guide for Effectiveness and Comparative Effectiveness Reviews*.[29] We will examine the following four domains: risk of bias, consistency, directness, and precision. For each key outcome for each comparison, we will assign an overall evidence grade based on the ratings for the individual domains. The overall strength of evidence will be graded as "high" (indicating high confidence that the evidence reflects the true effect and further research is very unlikely to change our confidence in the estimate of effect); "moderate" (indicating moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effect and may change the estimate); "low" (indicating low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effect and is likely to change the estimate); and (4) "insufficient" (indicating that evidence is either unavailable or does not permit estimation of an effect). The body of evidence will be graded independently by

two reviewers; disagreements will be resolved through discussion, or third-party adjudication, as needed.

G. Assessing Applicability

Applicability can be affected by differences between what occurs in trial settings and what happens in everyday circumstances. In this CER, applicability could potentially be limited by the following:

- Narrow eligibility criteria.
- Exclusion of patients with comorbidities.
- Doses used in trials that may not reflect what is used in clinical practice.
- Duration of followup and monitoring practice.
- Use of less-effective comparator treatment could exaggerate benefits of intervention therapy.
- Setting could affect standard of care.

We will extract and present data on both study and patient characteristics that may limit applicability. We will evaluate applicability of individual studies and then evaluate the applicability of the whole body of evidence.

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VI. Definition of Terms

Not applicable.

VII. Summary of Protocol Amendments

In the event of protocol amendments, the date of each amendment will be accompanied by a description of the change and the rationale.

VIII. Review of Key Questions

For all EPC reviews, key questions were reviewed and refined as needed by the EPC with input from Key Informants and the Technical Expert Panel (TEP) to assure that the questions are specific and explicit about what information is being reviewed. In addition, for Comparative Effectiveness reviews, the key questions were posted for public comment and finalized by the EPC after review of the comments.

IX. Key Informants

Key Informants represent a variety of stakeholder groups that are the end users of research, including patients and caregivers, practicing clinicians, relevant professional and consumer organizations, purchasers of health care, and others with experience in making health care decisions. Within the EPC program, the Key Informants provide input into identifying the Key Questions for research that will inform healthcare decisions. The EPC will solicit input from Key Informants when developing questions for systematic review or when identifying high priority research gaps and needed new research. Key Informants will not involved in analyzing the evidence or writing the report and have not reviewed the report, except as given the opportunity to do so through the peer or public review mechanism

Because of their role as end-users, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. The TOO and the EPC will work to balance, manage, or mitigate any potential conflicts of interest identified.

X. Technical Experts

Technical Experts comprise a multi-disciplinary group of clinical, content, and methodological experts who provide input in defining populations, interventions, comparisons, or outcomes as well as identifying particular studies or databases to search. They are selected to provide broad expertise and perspectives specific to the topic under development. Divergent and conflicted opinions are common and perceived as healthy scientific discourse that results in a thoughtful, relevant systematic review. Therefore study questions, design and/or methodological approaches do not necessarily represent the views of individual technical and content experts. Technical Experts provide information to the EPC to identify literature search strategies and recommend approaches to specific issues as requested by the EPC. Technical Experts do not do analysis of any kind nor contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism.

Technical Experts must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Technical Experts and those who present with potential conflicts may be retained. The TOO and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

XI. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodological expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will, for CERs and Technical Briefs, be published three months after the publication of the Evidence report.

Potential Reviewers must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Invited Peer Reviewers may not have any financial conflict of interest greater than $10,000. Peer reviewers who disclose potential business or professional conflicts of interest may submit comments on draft reports through the public comment mechanism.

Approximately 6–7 experts in the field of headache and migraine will be asked to peer review the draft report and provide comments.

Appendix A: Summary table of pharmacological interventions for acute migraine

Generic name	Trade name(s)	Mode of administration
Agents for procedural sedation		
Ketamine[1]	Ketalar	IV
		IM
Ketofol	NA	IV
Propofol	Diprivan	IV
	Lusedra	IV
Anticonvulsant		
Magnesium sulfate	Magnesium sulfate	IV
		IM
Valproic acid	Depacon	IV
Antiemetic		
Metoclopramide[2]	Maxeran	IM
	Reglan	IM
		IV
Trimethobenzamide	Tigan	IM
	Tebamide	IM
Corticosteroids		
Betamethasone[3]	Celestone Soluspan	IM
Budesonide	Entocort EC	Oral
Cortisone	Cortone	Oral, IM
Dexamethasone	Decadron	IM, IV
Hydrocortisone[4]	Solu-Cortef	Oral
Methylprednisolone[5]	Medrol	Oral
	Depo-Medrol	IM
	Solu-Medrol	IV, IM
Prednisolone	Prelone	Oral
Prednisone	Deltasone	Oral
Ergots		
Dihydroergotamine[6]	D.H.E. 45	IV, IM, SQ
NSAID		
Ketorolac	Toradol	IV
		IM
Opioids		
Butorphanol[7]	Butorphanol tartrate	IV
		IM

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Buprenorphine	Buprenex	IM, IV
Fentanyl	Sublimaze	IM, IV
Hydromorphone	Dilaudid	SQ, IM, IV
Meperidine[8]	Demerol	IV, IM
Morphine	Apokyn	SQ
	Astramorph PF	IV
	DepoDur	IV
	Duramorph PF	IV
	Infumorph	IV
Nalbuphine	Nubain	SQ, IM, IV
Neuroleptics		
Chlorpromazine[9]	Largactil	IM
		IV
Droperidol	Inapsine	IV, IM
Haloperidol[10]	Haldol	IV*
		IM
Prochlorperazine[11]	Stematil (other modes available)	IV, IM
Triptan agents		
Sumatriptan	Alsuma	SQ
	Imitrex (other modes available)	SQ
	Sumavel DosePro	SQ
Other agents		
Promethazine	Phenergan	IV, IM

Discontinued trade names include: [1]Ketamine HCL; [2]Maxolon, Clopra, Clopra-"Yellow", Metoclopramide intensol, Metoclopramide HCL, and Reglan ODT; [3] Celestone; [4]Cortef, Cortef acetate, Delta-Cortef, Neo-Cortef, and Neo-Delta-Cortef; [5]Medrol Acetate, Neo-Medrol, and Neo-Medral Acetate; [6]Embolex; [7]Stadol; [8]Mepergan, Atropine and Demerol, and Meperidine and atropine sulfate; [9]Thorazine, Chlorpromazine hydrochloride intensol, Promapar, and Sonazine; [11]Compazine and Prochlorperazine. [10]The U.S. Food and Drug Administration states higher doses and intravenous administration of haloperidol appear to be associated with a higher risk of QT prolongation and torsades de pointes..

Appendix B: MEDLINE search terms and strategy

Title: Acute Migraine in Adults in Emergency Settings

Database: Ovid MEDLINE® <1948 to April Week2 2011>

Terms for migraine:

1. Migraine Disorders/
2. migraine with aura/
3. migraine without aura/
4. Headache/
5. exp Headache Disorders/
6. migrain$.mp.
7. (headach$ or head-ach$).tw.
8. (cephalgi$ or cephalalgi$).tw.
9. or/1-8

Terms for drugs used to treat acute migraine

10. exp serotonin 5-HT1 receptor agonists/
11. sumatript$.mp.
12. zolmitript$.mp.
13. rizatrip$.mp.
14. eletript$.mp.
15. naratript$.mp.
16. almotript$.mp.
17. frovatript$.mp.
18. exp ergot alkaloids/
19. dihydroergotami$.mp.
20. DHE.tw.
21. ergotami$.mp.
22. exp analgesics, non-narcotic/
23. acetaminophen.mp.
24. (acetaminofeno or acetominophen or apap or asetaminofen or paracetamol or paracetamolis or paracetamolum or parasetamol or parasetamoli).tw.
25. exp anti-inflammatory agents, non-steroidal/
26. (NSAIA? or NSAID?).tw.
27. (non?steroidal adj anti-inflammator$).tw.
28. aspirin.mp.
29. (acetylsalicylic acid or ASA).tw.
30. diclofen$.mp.
31. (diklofen$ or diclophen$).tw.
32. ibuprofen$.mp.
33. ibuprofeeni.tw.
34. (ketoprof$ or dexketoprofeno).mp.
35. ketorola$.mp.
36. naprox$.mp.
37. naprok$.tw.
38. exp analgesics, opioid/
39. exp narcotics/
40. butorphanol$.mp.

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41. butorfanol$.tw.
42. codein$.mp.
43. (codeina or codeine or codeinum or kodeiini or kodein or kodeina or kodeinas or methylmorphine or metilmorfina or morphine methyl ether).tw.
44. meperidin$.mp.
45. (pethidin$ or petidiinihydrokloridi or petidin$ or petidinhydroklorid or petydyny).tw.
46. nalbuphin$.mp.
47. nalbufin$.tw.
48. tramadol$.mp.
49. propofol$.mp.
50. disoprofol.tw.
51. ketamin$.mp.
52. valproic acid/
53. (acide valproique or acido dipropilacetico or acido valproico or acidum valproicum or dipropylacetic acid or DPA or kyselina valproova or natrii valproas or natrio valproatas or natriumvalproaatti or natriumvalproat or natrium-valproat or valproat$ or valproic acid or valproiinihappo or valproik asit or valproine rugutis or valproinsav or valproinsyra).tw.
54. exp antiemetics/
55. exp Phenothiazines/
56. chlorpromazin$.mp.
57. (klooripromatsiini$ or klorpromazin$ or aminazine or chlor#promaz$).tw.
58. promethazin$.mp.
59. (prometatsiini or prometazin or prometazina or promethazinum).tw.
60. methotrimeprazin$.mp.
61. (levomeproma$ or lewomepromazyny).tw.
62. prochlorperazin$.mp.
63. (chlormeprazine or prochlorpemazine or prochlorperazin$ or proklooriperatsiini or proklorperazin).tw.
64. ondansetron$.mp.
65. droperidol$.mp.
66. metoclopramid$.mp.
67. metoklopramid$.tw.
68. domperidon$.mp.
69. exp histamine h1 antagonists/
70. diphenhydramin$.mp.
71. (benzhydramin$ or difenhidramin$ or difenhydramiinihydrokloridi or difenhydramin$ or dimedrolum).tw.
72. dimenhydrinat$.mp.
73. (chloranautine or dimenhidrinat$ or dimenhydramina or dimenhydrina$ or diphenhydramin$).tw.
74. butalbital$.mp.
75. (alisobumalum or allylbarbit$ or butalbitaali or butalbitalum or itobarbital or tetrallobarbital).tw.
76. Botulinum Toxins, Type A/
77. (Botuliinitoksiini tyyppi A or Botulinum Toxin Type A or Botulinum A Toksini or Toxin typ A mot botulism or Toxina botulinica A or Toxine botulinique type A or Toxinum Botulinicum Typum A).tw.

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78. lidocain$.mp.
79. (lidokaiini or lidokain$ or lignocain$).tw.
80. Xylocain$.tw.
81. oxygen.mp.
82. nitric oxide/ or nitrous oxide/
83. ((nitric or nitrous) adj oxide).tw.
84. magnesium sulfate/
85. (magnesium adj (sulfat$ or sulphat$)).tw.
86. drug therapy, combination/
87. drug combinations/
88. combined modality therapy/
89. placebo$.mp.
90. (pharmacologic adj manag$).tw.
91. (abortive adj therap$).tw.
92. **or/10-91**

Terms for corticosteroids used to treat acute migraine

93. exp glucocorticoids/
94. glucocorticoid?.tw.
95. (corticosteroid? or steroid$).tw.
96. betamethason$.mp.
97. (beetametasoni or betadexamethasone or betametason$ or betametazon$ or flubenisolon$).tw.
98. dexamethason$.mp.
99. (deksametason$ or desamethason$ or dexametason$ or dexametazon or dexamethason$ or hexadecadrol).tw.
100. hydrocortison$.mp.
101. (cortisol or hidrocortisona or hidrokortizon$ or hydrocortisonum or hydrokortison$ or hydrokortyzon).tw.
102. methylprednisolon$.mp.
103. (meilprednizolon or methyl-prednisolon$ or metilprednisolon$ metilprednizolonas or metylprednisolon or metyyliprednisoloni).tw.
104. prednisolon$.mp.
105. (deltahydrocortisone or metacortandralone or prednizolon$).tw.
106. prednison$.mp.
107. (deltacortisone or deltadehydrocortisone or metacortandracin or prednizon$).tw.
108. triamcinolon$.mp.
109. (fluoxiprednisolonum or triamcynolon or triamsinoloni).tw.
110. **or/93-109**
111. **or/10-109**

Terms for parenteral administration of medications

112. Injections, Intramuscular/
113. Injections, Intravenous/
114. Injections, Subcutaneous/
115. Infusions, Intravenous/
116. Infusions, Parenteral/
117. (IM or intra?muscular$).tw.
118. (IV or intra?venous$).tw.

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119. (SC or subcutan$ or sub-cutan$ or sub-cu?).tw.
120. (parenteral$ adj2 (inject$ or administ$ or therap$ or treatment?)).tw.
121. **or/112-120**

Terms for emergency/acute care

122. Emergency Treatment/
123. Emergency Service, Hospital/
124. Emergency Medical Services/
125. Emergencies/
126. Ambulatory Care Facilities/
127. Community Health Centers/
128. exp Outpatient Clinics, Hospital/
129. Community Health Services/
130. exp General Practice/
131. Primary Health Care/
132. ((emerg or emergenc$) adj3 (department? or ward? or service? or unit? or room? or hospital? or care or medicin$ or treatment? or admission?)).tw.
133. ED?.tw.
134. ER?.tw.
135. (ambulatory adj2 (clinic? or care or centre? or center? or service?)).tw.
136. ((out-patient or outpatient) adj2 (clinic? or care or centre? or center? or service?)).tw.
137. (community adj2 (service? or care)).tw.
138. (primary adj2 care).tw.
139. (urgent adj2 care).tw.
140. ((pain or walkin or walk-in) adj2 (clinic? or centre? or center? or service? or unit?)).tw.
141. or/122-140
142. and/9,111,121,141