Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Acute Migraine Treatment in Emergency Settings*

Draft review available for public comment from July 18, 2011 to August 15, 2011.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

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Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General	This report leaves the clinician with little direction as to how to better treat a migraine headache in the ED. It does however summarize well the RCT's evidence. It fails to include certain key information as it did not incorporate adverse event data from the FDA. Key questions are very well stated and appropriate.	The limitations of the evidence base precluded us from making more definitive conclusions. It was outside the scope of this review to search the FDA's adverse events database.
Peer Reviewer #2	General	This is the first time I have read one of the AHRQ reports. The structure of the report is set up to be redundant and lengthy. For instance, the Executive Summary and the Summary and Discussion sections are in some places identical with identical tables. I am not sure this adds any value to the reader. However, this is not necessarily within the authors' control. The authors appeared to do a thorough review of the literature. Having just reviewed this same topic myself, I am aware of how difficult it is to gather good data out of the available articles.	Thank you for your comment.
Peer Reviewer #3	General	The content of the review is clinically pertinent and will target the audience appropriately	Thank you for your comment.
Peer Reviewer #4	General	The report is highly clinically relevant to emergency care and contains explicit information.	Thank you for your comment.
Peer Reviewer #5	General	Too long. 69 articles were reviewed in 218 pages. You probably could have just reprinted all 69 articles instead. No one outside of the committee will read this report, except in abstract form.	This is a technical report that follows the publication guidelines of AHRQ's EPC Program and includes the requisite level of detail.
Peer Reviewer #6	General	This AHRQ Evidence Based Practice Center (EPC) review evaluates the comparative effectiveness and side-effect profiles for commonly prescribed parenteral migraine headache abortive therapies in emergency department populations. The exhaustive search strategies and strict methodology employed ensure a comprehensive, minimally biased product for all stakeholders. The implications for future research are an insightful and requisite portion of this manuscript that will be essential reading for future investigators and funding organizations. However, several editorial additions to this review will further improve the usefulness of the final product for these same stakeholders. These editorial suggestions are highlighted in the comments below using the page numbers from the PDF document.	Thank you for your comments. We have addressed the specific comments itemized by the peer reviewer.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	As an emergency physician, I really disliked the fact that you included "equivalent" non-ED settings, one of which was in Serbia. This review is for emergency settings, which I equate with emergency departments. "Equivalent" settings, which I don't believe were ever defined, are most likely NOT equivalent to a typical academic (where I am presuming most of these studies were performed) ED setting. I personally would want to eliminate these 'equivalent ED' studies from this review.	We have defined “equivalent settings” in both the executive summary and methods section of the review. We found that trials that took place in headache/pain clinics or neurology departments provided valuable information on first line parenteral treatment of acute migraine. We have discussed the inclusion of non-EDs settings in the applicability sections of the executive summary and the review.
Peer Reviewer #7	General	You use multiple terms, seemingly interchangeably, and this was a little confusing to me. For example, you discuss neuroleptics vs phenothiazines vs dopamine receptor antagonists. Some of these categories are subgroups of the others but there doesn't seem to be much consistency in how the terms are used. Perhaps pick one and stick with it?	We understand that many drugs have different mechanisms of action (e.g., an antiemetic can have analgesic effects). However, we had to choose what we believed to be the most fitting class in which to categorize each drug. The classifications we used were determined by our clinical leads in consultation with the Technical Expert Panel (TEP). We have reviewed the report carefully to ensure that we have been consistent with our classification and terminology.
Peer Reviewer #7	General	It doesn't seem that you consider the dose of medication. For example, in the US the typical dose of metoclopramide is 10 mg. But I believe that some of the studies using metoclopramide use 20mg, or double the dose. That would probably bias the outcomes in favor of metoclopramide and likely increase the side effects.	We appreciate these concerns; however, there were an insufficient number of studies to perform meaningful subgroup comparisons. Moreover, most studies in a comparison used a standard dose (e.g., most of the metoclopramide papers used 10 mg IV; where the doses were different, we did not pool).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	General	The division of migraine medications seems a little confusing to me. It seems when you state antiemetic, you mean metoclompramide and nothing else. Yet emergency physicians use prochloperazine, promethazine, droperidol, etc, primarily as antiemetics and secondarily as anti-migraine medications.	The investigators, with input from the Technical Expert Panel, spent much time debating how to classify the interventions and developing the approach for the report. There will be no ideal classification system, especially considering the potential different mechanisms of the agents involved. We specifically separated metoclopramide from the neuroleptics since clinicians appear to treat these agents differently, and we felt this separation would help in the report's generalizability. We have re-named the "antiemetic" section "metoclopramide."
Peer Reviewer #7	General	Key questions do seem appropriate and explicitly stated.	Thank you for your comment.
Peer Reviewer #7	General	The title made this seem very clinically meaningful, but after reading it, it was actually a little disappointing in terms of what I came away with.	Thank you for your comment.
Peer Reviewer #7	General	Over the years, various migraine medications have been unavailable due to shortages, etc. At one point I was using promethazine (Phenergan) to treat all my ED migraine patients. Maybe I missed it but where are the studies for this medication?	Promethazine (Phenergan) was included in Table 1 under the "other agents" portion as one of the drugs we included in this review.
Peer Reviewer #8	General	The target population and key questions are clearly stated. The report reflects the lack of strong evidence favoring a specific medical therapy for acute management of migraine headache.	Thank you for your comment.
Peer Reviewer #9	General	The report has limited utility for clinicians due to substantial problems with the organization of the report.	Our report follows the template outlined in the publication guidelines of the AHRQ EPC Program. We have reviewed the entire document and have made changes to improve the clarity.
Peer Reviewer #10	General	The study addresses a clinically meaningful subject that has not just treatment implications but also potential quality of care impact. The key questions are clinically relevant and clearly stated. Unfortunately the conclusions are hampered by the either paucity of studies to draw from and/or the quality of the studies in some cases.	Thank you for your comment.
Peer Reviewer #12	General	Ver meaningful/useful to the practicing emergency physician. Answers some very important and recurring questions. The audience is not very well defined, but is inferred by the title ancd introduction. The questions are well stated and answered. It might be fair to specify in the title that the review concerns only adults.	Thank you for your comment.

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Peer Reviewer #13	General	Comprehensive and carefully written. Key questions are meaningful from the perspective of the interface between the patient and the acute health care system.	Thank you for your comment.
Peer Reviewer #1	Executive summary	Executive summary line 53. Opioids do not 'cause ' relapse; rather they are associated with a higher risk of relapse. Similarly it would be very hard (if not impossible) to prove that a single dose of an opioid for a migraine headache in the ED leads to physical dependence. This sentence needs to be rewritten, as will similar statements elsewhere in the text (line 48 of page 29/218 of document) Taxonomy in pain research is inconsistent (see my comments below about recurrence); this should be elucidated in the Introduction. Similarly, although the IHS definition of a migraine is provided, there is little discussion about ..whether patients enrolled always met those criteria or whether other patients with benign headache could have been included.	We have changed the wording as follows: "their recognized ability to cause dependence and association with a higher risk of headache relapse." We do not make the claim that a single dose of an opioid leads to physical dependence. In the description of included studies section, we added a statement that "in 43 (61%) studies, migraine was classified using criteria established by the International Headache Society."
Peer Reviewer #2	Executive summary	In the Executive Summary, drugs are loosely discussed in terms of neuroleptics, metoclopramide, and antihistamines (without specific drugs listed), while in the text there is also mention of "anticholinergics" (presumably benztropine? Or diphenhydramine?)	We had many discussions about the terms used to describe agents that are used to prevent akathisia. We have reviewed the report and have standardized our terminology for these agents. Several agents have both antihistamine and anticholinergic properties; however, as you suggest, we have standardized our terminology using "anticholinergics."
Peer Reviewer #8	Executive summary	ES-1 Para 2 Spelling out "percent" may be the standard approach for AHRQ reports (e.g. "seven percent"),but for easy readability recommend the use of the % symbol throughout the text (or at least the abstract).	We follow AHRQ's publication and style guidelines for standardized reporting.
Peer Reviewer #8	Executive summary	ES-1 Para 3 Missing comma after "in more recent studies".	Comma was added as per your suggestion.
Peer Reviewer #8	Executive summary	ES-2 Key Q1 Change "active treatment" to "active therapy". Similar change for first paragraph Page 102.	We are not able to change the wording of the key questions at this stage of the review.

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Peer Reviewer #4	Structured abstract	"The risk of sedation was 17 percent. The odds of developing akathisia was 10 times greater than with placebo." is repeated within the abstract on lies 22 and 25. If this is not an error, I suggest changing the wording slightly in one of them to avoid the confusion.	This was not an error, as the first statement is referring to metoclopramide vs. placebo while the second statement refers to neuroleptics vs. placebo. The numbers were 9.35 and 10.7 respectively and were both rounded to 10. We have changed these numbers so they correspond with Figure 42 (Mixed treatment analysis of studies that report akathisia as a side effect). We have also reworded the abstract to improve clarity.
Peer Reviewer #8	Structured abstract	The focus of the review on parenteral routes of administration is made clear in the objective but should be reemphasized in the Conclusion. Similarly, consider adding "adult" somewhere in the Conclusion.	The last sentence of the conclusion reemphasizes the focus of the review on parenteral routes of administration. We have replaced the word "patients" with "adults".
Peer Reviewer #1	Introduction	Table 2 lists the trade name of prochlorperazine as Stematil, which is true for Canada. The trade name in the USA is Compazine	We have added Compazine to Table 1 which summarizes the pharmacological interventions for acute migraine.
Peer Reviewer #2	Introduction	Page 2, line 8: Chronic migraine is defined as headache on ≥15 days per month at least 3 months.	We have changed this to ">15 days".
Peer Reviewer #2	Introduction	Table 1 on page 4 (Summary of pharmacological interventions for acute migraine) I would recommend adding "Thorazine" as a trade name for chlorpromazine (this is the US brand name). Also, "Compazine" should be added as a trade name for prochlorperazine. Lastly, I am not sure why promethazine is listed as "other." I understand that it is somewhat difficult to classify as it is a weak neuroleptic, an antiemetic, and has some antihistaminergic properties…It either needs to be listed with the antiemetics or neuroleptics (usually it is listed with the neuroleptics with prochlorperazine). Also, antihistamines (hydroxyzine) and lidocaine are not listed on this table, though they are later discussed—these might be reasonable for the "other" category…	Thank you; these revisions were added to the table. The investigators, with input from the Technical Expert Panel, spent much time debating how to classify the interventions and developing the approach for the report. There is no ideal classification system, especially considering the potential different mechanisms of the agents involved.
Peer Reviewer #2	Introduction	Then on page 4, there are "antiemetics" (metoclopramide and trimethobenzamide), neuroleptics (chlorpromazine, droperidol, haloperidol, and prochlorperazine), and promethazine is listed under "other." (as stated above, this needs to be categorized as either an antiemetic or a neuroleptic; usually it is categorized as a weak neuroleptic).	Given the number of comments about antiemetics, we have deleted the antiemetics grouping and replaced it with metoclopramide. We have added a sentence in the main report explaining this decision (in the metoclopramide section of the results).
Peer Reviewer #3	Introduction	None.	Thank you.
Peer Reviewer #4	Introduction	Concise with informative diagrams.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #5	Introduction	repetitive.	This is a technical report that follows the publication and style guidelines of AHRQ's EPC Program.
Peer Reviewer #6	Introduction	This is a succinct summary of the costs and patient-centric impact of migraine headaches with references implying significant practice heterogeneity. Three domains of migraine headache need to be reviewed in more details. First, some attempt to quantify the practice heterogeneity in the introduction is necessary to persuade target audiences to read further. For example, after nearly two decades in emergency medicine I have not personally witnessed triptans or DHE used for abortive therapy in emergency department (ED) settings. Second, the authors should include sub-type epidemiology of headaches in the ED. How often do ED physicians use International Headache Associations to classify undifferentiated headaches as "migraine" versus other types of headache? What proportion of headaches in the ED are "migraine" versus cluster, post-concussive, tension, etc.? How accurate are ED physicians are differentiating "migraine" headaches from other headache sub-types? Does it matter (therapeutically, prognostically) if "migraine" headaches are mislabeled as other headache sub-types (or vice versa)? While diagnostic accuracy is not the primary objective of this AHRQ review, without a transparent understanding of how well or poorly emergency personnel currently differentiate migraine headaches readers will not be able to efficiently apply these findings to their patients. One recently developed resource for evidence-based diagnostics to benefit future AHRQ reviews for emergencies conditions is the Academic Emergency Medicine Evidence Based Diagnostics section. Third, what is the role of oral agents (anti-emetics, neuroleptics, etc.) when prescribed either primarily to abort the current headache or as prophylaxis at discharge? I realize that the intent of this review is to focus on the comparative effectiveness of parenteral agents, but most of the practice heterogeneity that I see involves the misuse of oral agents with the presumption that they are just as efficacious as the parenteral form of the same medication. The authors must justify their focus on parenteral agents and provide some references to the (lack	The report did not look at costs, but rather proxies such as health services utilization. Several trials included in the review that assessed DHE and triptans were conducted in North America. In the description of included studies section, we added a statement that "in 43 (61%) studies, migraine was classified using criteria established by the International Headache Society." We have also included a discussion of this in the applicability section. Interesting point, but beyond the scope of this review. We focused the review on parenteral interventions because the large majority of patients presenting to the ED have already failed oral medications and other home remedies. In addition, most patients presenting to the ED are experiencing nausea and/or vomiting so continued oral interventions can prove to be futile. Lastly, the rapid onset and

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		of?) efficacy of oral agents for acute migraine therapy.	efficacy of parenteral agents is appealing to both patients and clinicians. We have added this to the Key Question section of the introduction.
Peer Reviewer #7	Introduction	You give the IHS criteria for migraine, although you don't specify if this is for common or classic.	We have added this information to the introduction under Diagnosis and Treatment (p. 1)
Peer Reviewer #8	Introduction	The use of the term “neuroleptics” is inconsistent. For example, under the Acute Headache Pain and Symptoms section (P2), drug classes are described but neuroleptics are not mentioned. On the other hand, in the Executive Summary (ES-5) section, neuroleptics are described as a drug class. Readers may find this confusing, especially since clinicians do not commonly use this term. Given the effectiveness of these agents as described in the Results for Key Q1 and displayed in the Forest plots, it may be helpful to define clearly describe what agents qualify as a "neuroleptic" in the Introduction.	Thank you for this comment. We have attempted to standardize the use of these terms throughout the report.
Peer Reviewer #10	Introduction	The introduction presents a clear picture of the epidemiology and current practice patterns regarding migraine management in the emergency department. It could speak more to some of the factors that drive practice patterns (e.g. defensive medicine).	The reason for physician decision making is indeed important; however, was well beyond the scope of the review.
Peer Reviewer #12	Introduction	Introduction good - reasonably detailed, but not too long.	Thank you for your comment.
Peer Reviewer #13	Introduction	"Most patients were female aged between 30 and 40 years." should be rephrased, along the lines of "Most patients were female, and the mean age was generally between 30 and 40 years."	Changed this statement as per your suggestion.
Peer Reviewer #1	Methods	Methods for searching the literature were robust inclusion/exclusion criteria were fair as it was not clear if a migraine diagnosis was based on IHS criteria or on clinician impression the definition of recurrence needs to be properly defined	Thank you for your comment. We added a statement in the description of included studies section that stated, “in 44 studies, migraine was classified using criteria established by the International Headache Society.” We defined headache recurrence in Table 2 (Eligibility criteria for this review) as “headache relieved in the ED and recurring within the following period”.
Peer Reviewer #2	Methods	This appears to be fine.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Methods	In the methods section Table 2, these drugs are reclassified as "phenothiazines" (including chlorpromazine, prochlorperazine, and droperidol) with no mention of the others. Importantly, droperidol is not a phenothiazine, it is a butyrophenone.	Thank you for this observation and correction; we have revised the report to consistently use the term neuroleptics.
Peer Reviewer #3	Methods	The I/C are defined. The search strategies are appropriate. Stats are appropriate	Thank you for your comment.
Peer Reviewer #4	Methods	A comprehensive search strategy described well enough for replication. Again, explicit details are provided precluding confusion or ambiguity.	Thank you for your comment.
Peer Reviewer #5	Methods	Good. Do you really have to mention what type of spreadsheet program (Excel) was used? That is a minor point, but it illustrates there is too much minutia in this report.	No change.
Peer Reviewer #6	Methods	On page 18, KQ5 and KQ6 should provide additional details about what subpopulations were considered. When reading KQ2, knowledgeable readers will be wondering about the role of steroid dose and timing (in relation to the duration of headache). When they reach KQ5 and KQ6, these issues are addressed but one needs to read through to page 123 and page 143 to realize that this review did contemplate the dose and timing of steroids to prevent migraine recurrence. Some readers might not read that far and these important details need to be more transparent. On a similar note, many readers will be confused in the first 30-pages of this document by the nomenclature used to describe the medication classifications. For example, which agents are "anti-emetic" and which are considered neuroleptics or phenothiazines? The authors do clarify these terms in Table 1 on page 31, but some readers might not make it that far. This table labeling the classification nomenclature used should appear earlier in the manuscript.	The subpopulations are included in the key questions 5 and 6. These were identified a priori in consultation with the Technical Expert Panel. The subgroup analysis for steroid dose and timing were post hoc analyses and are reported as such in the results for KQ2 Thank you for this suggestion. We have added the "Summary of pharmacological interventions for acute migraine" table into the executive summary (Table A).
Peer Reviewer #6	Methods	What are the potential harms of "non-evidenced based therapy" or "significant practice variability"? I understand what they are, but the authors should endeavor to be transparent to emphasize the potential benefits of this high-quality review.	We included references to studies that identified practice variability among EDs, including the range of agents used & use of non-evidence-based therapy. The potential benefits to standardizing care and practicing evidence-based medical care are presented in these referenced articles.
Peer Reviewer #6	Methods	Page 24: Typo on line 30 "95 confidence interval" is missing "percent".	Thank you; correction has been made.

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Peer Reviewer #6	Methods	Page 29: How often are HIS guidelines used to diagnose migraines in ED settings?	In the description of included studies section, we added a statement that "in 43 (61%) studies, migraine was classified using criteria established by the International Headache Society."
Peer Reviewer #6	Methods	Page 30: It would be extremely helpful and motivating to provide references for (or specific examples with references) where the "synthesis of this literature could lead to more standardized care".	In the discussion section of the report we have highlighted the use of IV dexamethasone in prevention of headache recurrence. This is one example of synthesis of literature leading to clear evidence to guide practice.
Peer Reviewer #6	Methods	Page 31: Table 1 should include doses. Please consider amending the label of this table to indicate that these are all FDA-approved uses for these agents.	Dosages used in individual studies are presented for every intervention in the patient and study characteristics tables in the results section. We have also indicated in the text that many of these agents are used off-label to treat acute migraine.
Peer Reviewer #7	Methods	I have no experience in this area and cannot really comment on the statistical methods and search strategies. I am curious why cohort studies and non-randomized trials were included. I found this initially confusing as I think no cohort studies were actually included in the analysis. Similar to my complaint of including 'equivalent' ED settings, I personally would have preferred this analysis eliminate the non-randomized trials.	We set out to include cohort and nonrandomized studies; however, no cohort studies met our inclusion criteria.
Peer Reviewer #7	Methods	Table 2 states one of the outcomes is a 10-point verbal scale. This is likely an 11-point verbal NRS (numerical rating scale). It is 11-point because you need to include zero.	The authors refer to the scale as a 10-point scale; we did not change their wording. Statistically it makes no difference since both the 10-point and 11-point scales are treated as continuous variables.
Peer Reviewer #8	Methods	The inclusion and exclusion criteria are clearly outlined, however, it is not made explicit if studies that included both adult and pediatric patients were excluded or if there was an attempt to perform subgroup analysis of adult subjects in such a studies (maybe there were none).	In the "Inclusion and Exclusion Criteria" of the methods section, we stated "Studies that enrolled children or adolescents were included only when at least 80 percent of patients were ≥18 years of age, or when subgroup analyses for adult patients were provided."
Peer Reviewer #8	Methods	Migraine headache outcomes are difficult to measure but the report provides clear justification for the patient-important outcomes in the acute care setting.	Thank you for your comment.
Peer Reviewer #8	Methods	The search strategy is well delineated and comprehensive. The statistical methods are clearly described and appropriate.	Thank you for your comment.

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Peer Reviewer #9	Methods	Reasonable inclusion criteria.	Thank you for your comment.
Peer Reviewer #10	Methods	The inclusion/exclusion criteria are appropriate. The search strategies are clearly stated as are the outcome measure definitions. The statistical methods are standard for this type of analysis. If possible, it would be meaningful to know duration of headache prior to treatment as duration of headache does effect abortive medication efficacy.	Duration of headache was only reported in 27/71 studies. Where reported, this information is included in the patient and study characteristics tables in the results section.
Peer Reviewer #12	Methods	I thought all of these were well done. The exclusion of pediatric headaches (if <80% were >18) may disappoint some readers - hence my suggestion that maybe the 'adult' focus should be mentioned in the title.	The title cannot be changed.
Peer Reviewer #13	Methods	clear and explicitly stated	Thank you for your comment.
Peer Reviewer #1	Results	Page 49/218 In the comparative studies between metoclopramide and neuroleptics there is no discussion of dose equivalence, making interpretation of comparators difficult at best. Were studies giving relatively higher doses of one than the other, providing bias? This would also impact the interpretation presented in Table 5.	We reported the dose of metoclopramide in the text in this section (as well as in the table of patient characteristics). The different doses did not explain the heterogeneity, although there were only 4 studies. Future research may help to determine the role of dose. We have graded the SOE as “low” indicating “Low confidence that the evidence reflects the true effect. Further research is likely to change the confidence in the estimate of effect and is likely to change the estimate.”
Peer Reviewer #1	Results	Page 56/218. Since this is not a meta-analysis then outcomes from all trials could have been discussed. For example, there is at least one study that showed that 24 recurrence rate with prochlorperazine was only 8% yet this is not presented – only that ‘fewer patients with prochorperazine than those with placebo had headache recurrence. It needs to be clearer how much less the recurrence rate was	The headache recurrence section of the neuroleptics section reports results for chlorpromazine vs. placebo and droperidol vs. placebo. Risk ratios for both comparisons are provided.

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Peer Reviewer #1	Results	Page 66/218 (and elsewhere). I would suggest the term 'recurrence' needs to be better defined in the discussion. 'Recurrence' suggests the headache was completely relieved and the pain came back whereas 'persistence' means the headache never resolved (even though it improved). Since most patients with migraine leave the ED with some pain still present and do not define if the headache resolved completely, most statements about recurrence at 24 hours are probably inaccurate.	This is an interesting issue in the review. Patients who had limited headache relief in the ED would be classified at followup as ***persistent*** if their pain was severe. Patients who had incomplete headache relief in the ED would be classified at followup as ***relapse*** if their pain was severe. Conversely, patients who had complete headache relief in the ED would be classified at follow-up as ***recurrence*** (defined in Table 2 eligibility criteria for this review: as "headache relieved in the ED and recurring within the followup period."). Unfortunately, this granular detail was missing in many reports, so we could not provide a more refined description than "relapse."
Peer Reviewer #1	Results	In the opioids section greater detail about opioid dosing would improve the discussion. While dosing for prochlorperazine to achieve good relief is fairly well established, the same cannot be said for opioids. They are titratable medications, yet in migraine studies were inevitably given as single doses, and usually (with meperidine) at a subtherapeutic dose (< 1mg.kg). To then discuss comparative studies without ensuring adequate dosing will inevitably result in invalid conclusions. Dosing should therefore be clear in tables such as Table 15, and discussion about therapeutic vs. subtherapeutic opioid dosing needs to be included.	This is an excellent point and we have added this to the limitations section by stating, "the therapeutic vs. subtherapeutic dosing variation may limit some comparisons". Also, note that dosages are presented for every intervention in the patient and study characteristics tables in the results section.
Peer Reviewer #1	Results	In the triptan section there does not seem to be reference to the sumatriptan – Cafergot (European Cafergot trial)migraine study that also had a placebo arm. It showed recurrence at 24 hours with triptans was worse than with placebo. Since Cafergot is an ergotamine but not DHE per se, should this not be present and distinct from the DHE/triptan discussion?	The study "A randomized, double-blind comparison of sumatriptan and Cafergot in the acute treatment of migraine. The Multinational Oral Sumatriptan and Cafergot Comparative Study Group" was not included because neither intervention was delivered parenterally.
Peer Reviewer #1	Results	Page 137/218. There is a section here reporting on chest symptoms. Given the adverse outcomes know from DHE and triptans would it not have been better for the reader to have the authors report on adverse event data submitted to the FDA? e.g. the number of deaths reported from use of triptans since their introduction to the market. Otherwise the serious adverse event rate is under-reported to the readers	We have added the following sentence to the discussion/summary section for KQ 3. "Due to the select populations in trials, the potential for adverse effects of the triptans might be higher, especially for patients with vascular risk factors." It was outside the scope of this review to search the FDA's adverse events database.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	Results	The biggest issue that was a running theme through introduction, methods, results, etc, was a lack of consistency in the way that the neuroleptics/antiemetics were handled. Some examples are listed below. Because of the lack of consistency throughout the paper, after reading it, I was still not sure what the authors meant in text and graphs that discussed the efficacy of "neuroleptics."	Thank you for pointing this out. We have endeavored to make corrections throughout the document to rectify this concern.
Peer Reviewer #2	Results	In the results section (page 30), the neuroleptics are again discussed, with droperidol missing from the studies. Here, I would recommend including the following trial: Silberstein SD, Young WB, Mendizbal JE, Rothrock JF, Alam AS. Acute migraine treatmment with droperidol: A randomized, double-blind, placebo-controlled trial. Neurology 2003; 60(2): 315-321	Thank you. We have added this study to our review.
Peer Reviewer #2	Results	On page 34, when discussing neuroleptics versus other agents, the authors have listed lidocaine as a neuroleptic, and it is not one. On most other pages, they categorize lidocaine as one of the "orphan drugs" which I think is more appropriate. Also on page 34, they have listed olanzapine (an atypical antipsychotic) and methotrimetptrazine (a phenothiazine) for the first time in the neuroleptic category. Does this mean these were included in some of their "neuroleptic" summary statements/graphs?	Thank you for pointing out this error; we agree lidocaine is not a neuroleptic. We have made the correction to the document. Olanzapine is an atypical antipsychotic, and it has all of the same side effects as the neuroleptics. The exact mechanism for the antipsychotic properties is not clear. So, although it is not entirely accurate, we believe it is fine to classify it with the neuroleptics. Methotrimeprazine is a phenothiazine. Again, it is classed with phenothiazines like chlorpromazine and promazine.
Peer Reviewer #3	Results	The studies are well described. All of the figures and tables are good and describes the studies adequately.	Thank you for your comment.
Peer Reviewer #4	Results	The information is the results is overwhelming although I had difficulty finding the following information from the abstract for both metoclopromide and neuroleptics: "The risk of sedation was 17 percent. The odds of developing akathisia was 10 times greater than with placebo."	We agree there is a lot of information summarized. The risk of sedation is from the side effects section under both agents, and the reference to the 10 times greater akathisia is contained in the network meta-analysis. We have reworded this section to improve clarity.
Peer Reviewer #5	Results	Too long. The American Academy of Neurology can do similar Practice Parameters and susceeds in generating the report typically within a few journal pages.	We agree there is a lot of information summarized. This is the standard approach to reporting for the AHRQ's EPC Program.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Results	Key Questions beginning on page 45: Since this is a comparative effectiveness review, please explain the benefit of reporting placebo-controlled trials which clutter the document leaving the more important "agent versus active treatment" comparisons that constitute comparative effectiveness research harder to find.	We used the data from the placebo controlled trials in our network meta-analysis.
Peer Reviewer #6	Results	Page 50: In trying to find reference #101, it became apparent that this very long document is difficult to peruse in a clinically useful manner. There are multiple bibliographies/reference tables (pp 27-28, pp 153-158, pp 201-208). It would be helpful for readers to have one bibliography for the entire document and hyperlinks for the citations in the document either directly to the bibliography or to the PUBMED abstract.	The Executive Summary is a standalone document that requires its own reference list separate from the review.
Peer Reviewer #6	Results	Page 119: Did the mixed treatment analysis include adverse drug events? Since neuroleptics alone appear to be as effective as combination therapy, stakeholders' selections may hinge on side-effect profiles. If no difference in side-effect profiles or costs, this summary should seemingly make a stronger statement in favor of neuroleptics.	We conducted a mixed treatment analysis for akathisia (KQ4). There were not enough trials comparing the same drugs and reporting the same adverse effects to support a network meta-analysis for other adverse effects.
Peer Reviewer #7	Results	I would have liked to have seen another column in the various tables (such as table 6) that shows what was considered the minimum clincially significance in the primary outcome.	The MCID is debated in the literature. We have elected not to make this change.
Peer Reviewer #8	Results	The amount of detail is a bit overwhelming but the Forest Plots provide a nice visual summary of the results. The key questions are directly relevant to the practice of emergency medicine. I am not aware of any studies that were missed by the investigators.	Thank you for your comment.
Peer Reviewer #9	Results	Not clearly described. The routes of administration of agents needs to be clearly identified. For example, the routes of administration of opioids DHE not always clear in the text. See comments under f. clarity.	The routes of administration for every intervention can be found in the patient and study characteristics tables in each section.
Peer Reviewer #10	Results	The results sections are clearly written although it would be helpful to design a few summary tables that really highlight the most practical results of the analyses, to date what is the hierarchy for best available treatment in the ED setting	We have added a summary of strength of evidence (SOE) table in the executive summary that summarizes the SOE for all gradable outcomes. The table excludes any outcomes that were assessed to have "insufficient" SOE. The complete SOE tables with all gradable outcomes are presented in the discussion/summary section of the main report. These tables also present the effect estimates and 95% CI for each head to head comparison.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #12	Results	I did not repeat a search to see if any studies had been missed - the search strategy described was most satisfactory. The results presented were very clear and appropriate. Tables were excellent, with the 'mean difference' chart on the right very useful.	Thank you for your comment.
Peer Reviewer #13	Results	excellent detail and summaries. The potential for adverse effects of the triptans might be more explicitly stated with regards to vascular risk factors, and the careful exclusion criteria for these studies.	We have added a sentence in the discussion section for KQ 3 to address this point.
Peer Reviewer #1	Discussion/Conclusion	future research section clear implications are vague given the analysis provided No one can identify an optimal strategy or a treatment plan that combines optimal results with lowest possible AEs. I do not know if the authors could have done better however given the quality of the literature reviewed	Thank you for your comments.
Peer Reviewer #2	Discussion/conclusion	Discussion/ Conclusion: On page 121, they list promethazine as an “anticholinergic.” (line 6) The only study they referenced was one using diphenhydramine as the anticholinergic. Is this what they meant?	Yes, the reviewer has made the correct interpretation. We have endeavored to be consistent throughout the document with respect to anticholinergic agents.
Peer Reviewer #3	Discussion/conclusion	The conclusions are well sounded and appropriate.	Thank you for your comment.
Peer Reviewer #4	Discussion/conclusion	This report exposes the lack of evidence support the use of many commonly prescribed agents and definitely identifies multiple areas of future research.	Thank you for your comment.
Peer Reviewer #5	Discussion/conclusion	This could have been the entire manuscript	No change.
Peer Reviewer #6	Discussion/conclusion	Well summarized statement reviewing the applicability and limitations of the existing research before analyzing the priorities for future research efforts in this field. Once again, after reading this review, it would seem that neuroleptics should receive a more pronounced endorsement than they currently do.	Thank you for your comment. As appropriate, we have highlighted the results for neuroleptics in the abstract, ES and discussion/summary section of the main report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #7	Discussion/conclusion	I believe you overstate the significance of DHE in combination therapy in your conclusion. I personally have practiced in approximately 20 EDs in 4 different states and never once have given DHE, including with consultation from neurologists for patients who needed to be admittted for their migraine. On page ES-9, you state: 'In the mixed treatment analysis of pain relief, there was a clear indication that combinations of antimigraine medications (i.e. DHE in combo with either neuroleptics or metoclopramide....) outperformed other agents. Yet the data providing the evidence for this was post hoc, and you also state that the strength of evidence for the mixed treatment analysis was LOW and the risk of bias was moderate.	Our synthesis of the data is not affected by the fact that it was a post hoc analysis. In addition, we state the risk of bias rating so that readers can judge the results accordingly.
Peer Reviewer #7	Discussion/conclusion	I disagree with your statement that the results are generalizable to most ED patients given that most did not report on race or ethnicity. Since most of the studies are probably done at academic medical centers, the patient population may be poorer and more Hispanic, etc.	We have addressed this point in the applicability section of the main report.
Peer Reviewer #7	Discussion/conclusion	I do believe the future research section is clear and easily translated into new research.	Thank you for your comment.
Peer Reviewer #8	Discussion/conclusion	The multiple limitations identified in the systematic review are clearly described.	Thank you for your comment.
Peer Reviewer #8	Discussion/conclusion	The future research section is insightful, particularly the recommendation to study combination of agents vs. sequential administration given that this seems to be an area of practice substantial variation even within the same institution.	Thank you for your comment.
Peer Reviewer #8	Discussion/conclusion	In the Conclusion section (P 110), why is DHE combined with metochlopramide or neuroloptics (low strength of evidence) given the same emphasis as neuroloptics alone (moderate strength of evidence.	SOE for neuroleptics vs other active agents was insufficient (not moderate) for pain intensity (VAS). When compared with placebo, SOE was moderate. Our statement about DHE in combination with metocholpramide or neuroleptics and neuroloptics alone is based on the mixed treatment analysis that showed the same effect estimate (VAS for pain reduction) for both interventions.
Peer Reviewer #9	Discussion/conclusion	There is no mention of the use of opioids for the treatment of migraine--whether there is a role for them or not.	We summarize the results for opioids in the discussion section.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #10	Discussion/conclusion	The findings are clearly stated but a clean table of the major results would be helpful. There were no significant omissions to my knowledge. The limitations of the existing evidence due to risk of bias and variability between studies and the impact on conclusions was acknowledged. The future research section is clear. The suggestions for consensus on outcome measures and the need for comparative studies between studies are excellent. (p. 123)	We have included tables in the ES and the summary/discussion section of the main report to provide a summary of the major results (i.e., outcomes that were graded).
Peer Reviewer #12	Discussion/conclusion	The 'future research' section is excellent and will be a perfect platform for future migraine researchers to proceed from. This document will be very useful to practitioners (or, at least a shrt version), but more so to migraine reserachers! Limitations are well described and implications well stated.	Thank you for your comment.
Peer Reviewer #13	Discussion/conclusion	excellent	Thank you for your comment.
Peer Reviewer #1	Clarity and usability	No conclusions about practice decisions can be made other than to not use a placebo for migraines.	We disagree with this statement. Conclusions that may contribute to practice decisions can be found in the ES as well as the discussion and conclusion sections of the main report. For example, “Neuroleptic monotherapy or DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options”; “systemic corticosteroids effectively prevent relapses, especially in patients with prolonged headaches”. One can also use the mixed treatment analysis presented in Figure 31.
Peer Reviewer #2	Clarity and usability	Clarity and Usability: See comments in results section. Once again, because of the lack of consistency in the way neuroleptics were handled, I was unsure how to interpret the concluding statements/tables regarding neuroleptics	We have made changes throughout the document to be consistent with respect to neuroleptics agents.
Peer Reviewer #3	Clarity/usability	Structure and organization are great.	Thank you for your comment.
Peer Reviewer #4	Clarity/usability	This is an all-inclusive report with great detail and surpasses all all previous reviews.	Thank you for your comment.
Peer Reviewer #5	Clarity/usability	Too long to be of use to almost anyone.	We recognize the length is problematic; however, we have provided an abstract and an executive summary for readers who want a “clinical bottom line”. Those with greater interest in the granular detail will find the report helpful for generating new research ideas as well as clinical practice guidelines.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #6	Clarity/usability	There are multiple bibliographies/reference tables (pp 27-28, pp 153-158, pp 201-208). It would be helpful for readers to have one bibliography for the entire document and hyperlinks for the citations in the document either directly to the bibliography or to the PUBMED abstract.	The Executive Summary is a standalone document that requires its own reference list separate from the review.
Peer Reviewer #7	Clarity and usability	Although it is clear that the authors did a tremendous amount of work, I personally found this somewhat hard to read and follow.	We have tried to improve and clarify the report in response to specific comments made by other peer reviewers. However, this is a technical report and, by its nature, is complex.
Peer Reviewer #7	Clarity and usability	I believe the conclusions are overstated based on the evidence provided in the review. Ultimately it doesn't tell me something I don't already know (i.e. active treatment is better than placebo).	We disagree with this statement. Conclusions that may contribute to practice decisions can be found in the ES as well as the discussion and conclusion sections of the main report. For example, "Neuroleptic monotherapy or DHE in combination with either metoclopramide or neuroleptics appear to be the most effective options"; "systemic corticosteroids effectively prevent relapses, especially in patients with prolonged headaches". One can also use the mixed treatment analysis presented in Figure 31.
Peer Reviewer #8	Clarity and usability	The report is well written and the conclusions are as clear as the evidence allows. The lack of strong evidence makes it unlikely that the summary will inform policy such as quality measures but it should provide some guidance to clinicians.	Thank you for your comment.
Peer Reviewer #9	Clarity and usability	Poor clarity. For example, pethidine is used in the report. This is another name for meperidine. In addition, there are several issues that make this problematic. See the list below.	We added pethidine in brackets behind meperidine in Table 1, which summarizes the pharmacological interventions for acute migraine. Pethidine is the international nonproprietary name.
Peer Reviewer #9	Clarity and usability	Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and headache relapse.—What is the evidence that opioids, when given infrequently, leads to headache relapse? (See below where this statement is made again.)	We note "their recognized ability to cause dependence and association with headache relapse."

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Clarity and usability	Question—Were hand searches of the abstracts for the American Academy of Neurology? This is one of the largest neurology meetings in the world and specifically seeks and accepts abstracts on the topics of headache and pain? (Not mentioned on p. 15)	We hand searched conference proceedings (from 2008 to 2011) for scientific meetings identified by our clinical leads. We did not search the conference proceedings of the American Academy of Neurology. However, these conference proceedings are indexed in 3 of the electronic databases that we searched. Moreover, we searched the reference lists of all included studies. We are confident that did not miss any key trials.
Peer Reviewer #9	Clarity and usability	Trials should be designed and conducted to minimize bias where at all possible. Authors may find tools such as the CONSORT statements25 helpful in designing and reporting on randomized controlled trials.—Change the word authors to investigators.	Thank you for your comment. We changed the word “authors” to “investigators” as per your suggestion.
Peer Reviewer #9	Clarity and usability	Second, several treatments reported here provide insufficient evidence for continued use.—Many readers of this report will likely only read the summary so NAME the treatments that have insufficient evidence for continued use. Effective Health Care Page 24 of 218	We hope more people will want to read the entire report; however, we recognize the reviewer is reflecting the views of some busy clinicians. We have added examples (e.g., lidocaine, anithistamines, sodium valproate) to this statement in the ES and main report.
Peer Reviewer #9	Clarity and usability	Third, systemic corticosteroids effectively prevent relapses, especially in patients with prolonged headaches.—Is there a difference whether administered IV or IM?	While we did not present data by route of administration, this information is included in patient and study characteristic table at the end of this section. All but one study used IV; there was no difference for the one study that used either IV or IM.
Peer Reviewer #9	Clarity and usability	Migraines are thought to be initiated by stimulation and sensitization of the trigeminal peripheral nerves linked to intracranial vessels and meninges. Page 29. This is an incomplete, therefore somewhat misleading statement regarding the pathogenesis of migraine. SEE REVIEW PAPER BY CUTRER IN SEMINARS OF NEUROLOGY AND REWRITE. (Cutrer FM. Semin Neurol. 2010 Apr;30(2):120-30.)	We agree that the etiology and pathophysiology of migraines is complex and controversial. A full discussion of the issues is beyond the scope of this review. We have revised this section of the introduction.
Peer Reviewer #9	Clarity and usability	Although alternative phenothiazines exist, prochlorperazine is preferred due to its relatively improved side effect profile. Page 29 Improved compared to what?	We have changed the wording to state, “While alternative phenothiazines exist, prochlorperazine is usually preferred due to its efficacy and safety”. We have added references to support this statement in the ES and main report.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Clarity and usability	Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and headache relapse. Page 30. What is the evidence that opioids cause relapse? Especially if used infrequently?	We have changed the wording as follows: "Opioids are often used to treat acute migraine despite their recognized ability to cause dependence and their association with a higher risk of headache relapse."
Peer Reviewer #9	Clarity and usability	Table 3, page 39. Anxiety is NOT equivalent to mood change, moodiness.	We did not mean to imply these were equivalent; this is simply how some of the side effects were grouped.
Peer Reviewer #9	Clarity and usability	Antiemetics versus neuroleptics. Page 49. Why is does this heading have antiemetics in it? It appears that this looks at metoclopramide vs. antiemeteics. Furthermore, neuroleptics are antiemetics!!! VERY FEW STUDIES examined other anti-emetics such as ondansetron and trimethobenzamide.	We changed the heading from "antiemetics" to "metoclopramide" to reflect that all studies of antiemetics except one examined metoclopramide. We have highlighted the results for the one study that examined trimethobenzamide. We have explained how we present the results and our rationale at the beginning the results section for KQ 1.
Peer Reviewer #9	Clarity and usability	How was ketorolac administered? IV or IM? Any difference in effectiveness? What about opiates and neuroleptics?	Information on route of administration is presented in the patient and study characteristic tables in each section. There were too few studies to conduct sub-group analyses by route of administration.
Peer Reviewer #9	Clarity and usability	Opioids versus Active Agents—Confusing heading as some of the studies reviewed clearly describe a comparison of different opiates. Example: 1.1.2 Butorphanol versus Meperidine + Hydroxyzine	Table 15. opioids versus active agents shows that opioids were compared with various other agents including other opioids. The specific opioids are listed in the table.
Peer Reviewer #9	Clarity and usability	Opioids versus Active Agents—This is a misleading heading. Some of these studies. For example, some studies used meperidine plus hydroxyzine. Short-term side effects were commonly reported for patients receiving DHE. The most common side effects were skin and local reactions, sedation, digestive problems, nausea or vomiting, and chest symptoms.—Page 127. Are nausea and vomiting NOT digestive problems?? Why list these apart from "digestive problems"?	It was challenging to report and classify the myriad adverse effects that were reported by authors. We grouped the adverse outcomes in consultation with the technical expert panel (Table 3).

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #9	Clarity and usability	orphan agents (i.e. magnesium sulphate [MgSO4], valproate)—Why are these agents listed as "orphan agents"? There is no justification for this term in this manner.	We have added the following information in the ES and main report (description of included studies): "For the mixed treatment analysis, we identified a group of drugs that were not easily classified and were infrequently studied (i.e., hydroxyzine (Atarax), lidocaine, $MgSO_4$, sodium valproate, tramadol, and octreotide). We collectively referred to these drugs as "orphan agents".
Peer Reviewer #9	Clarity and usability	Muscle twitching is listed as an extrapyramidal side-effects	No change.
Peer Reviewer #9	Clarity and usability	Anxiety includes insomnia—this is not necessarily an anxiety-related symptom.	We grouped the adverse outcomes in consultation with the technical expert panel (Table 3).
Peer Reviewer #9	Clarity and usability	Preferred spelling of "sulphate" in U. S. is sulfate.	Thank you. We have changed "sulphate" to "sulfate" in all instances.
Peer Reviewer #10	Clarity and usability	The report is well structured and organized well. The main points are presented but a summary table would be helpful. The conclusions are potentially useful for practice to stem the overuse of narcotics and useful practices to lessen headache recurrence.	Thank you for your comment. We present summary tables of results in the executive summary and the discussion section of the report.
Peer Reviewer #12	Clarity and usability	Very well done - I actually enjoyed reading it (after initially being a bit intimidated by the size!)	Thank you for your comment.
Peer Reviewer #13	Clarity and usability	excellent	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Ed Heneveld	Executive summary	migraine headaches and the patients who suffer them are not homogeneous. this is the problem with trying to retrospectively find a solution. it very much matters how long the patient has been experiencing the headache and what has been tried prior to arrival and what has worked before. Droperidol is an excellent agent that the regulatory agencies have black boxed into near oblivion. it is important to focus on the symptoms the patient present with. if it has been going on for 12 or more hours, triptans are not likely to work. if the main feature is pain (not nausea) then analgesics (opiates, NSAIDs) are more likely to work. if the main feature is nausea/vomiting, then metocholrpropamide, or perchlorpromazine or droperidol is likely to benefit. if there are features of hysteria, anxiety, unusual stress, then the neuroleptics might work. sleep seems to reestablish the homeostasis needed to abort an attack. no one has looked to low dose ketamine followed by sedation with neuroleptics or even simple antihistamine +/- anti nausea meds to break the pain and induce sleep. nice summary of the evidence, but retrospectoscope will not solve this multifactorial problem.	We fully recognize that migraine is a complex topic and agree that personalized applications of evidence-based care are important clinical decisions. Many of these issues were beyond the scope of the project and we did not explore them in the detail required to support or rebut these comments. Droperidol was one of the interventions included in the review. Duration of headache was only reported in 27/71 studies; KQ 6 reports results of RCTs examining the effect of systemic corticosteroids to prevent headache relapse in the subgroup of patients with prolonged headaches.