Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Migraine in Adults: Preventive Pharmacologic Treatments*

Draft review available for public comment from April 12, 2012 to May 10, 2012.

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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
Reviewer 1	Quality of the Report	Superior	Thank you.
Reviewer 1	General Comments	Change all references to Botulinum toxin to onabotulinumtoxin A as this is the medication referenced in the articles sited and there are numerous other botulinum toxins which have not been studied.	We revised the report following your recommendations. We clarified that we used the WHO drug classification system that categorizes botulinum toxins under one category-M03AX01. The U.S. Food and Drug Administration approved Botox injection (onabotulinumtoxin A) for chronic migraine. Botulinum neurotoxin type A (marketed as BoNT-A; BOTOX, Allergan Inc.) was examined in several RCTs. Two RCTs examined Abobotulinumtoxin A (marketed as Dysport). We did not detect statistically significant differences in the reported outcomes among botulinum formulations.
Reviewer 2	**Comments for statistical methods for adults section**	The general statistical framework is fine. Here are some comments for the investigators to consider: One general question is that usually multiple methods are specified for the same situation; however, it is not clear which method was used in the analysis, why the multiple methods are needed and what are the criteria for the choice of methods. For example, for spare data, fixed effects MH RR, and Peto OR, double arcsine transformation and RE generalized nonlinear mixed effect models are mentioned. Why all these methods are needed? It is not clear which method is used for which condition. I don't see results from OR and double arcsine transformation in the text either about comparison between two treatments. The investigators may just pick one appropriate methods and stick with it. If there is the need to use alternative method, please provide justification. And then why a Bayesian OR is needed?	We synthesized sparse adverse effects data defined by comparing the results from several models. Models included random and fixed effects inverse variance methods, maximum likelihood methods, Peto odds ratio, double arcsine transformation for comparing two proportions and odds ratios from random-effects generalized nonlinear mixed-effect models. We tested robustness of the results from different models. In cases when very few studies were available to provide evidence from direct head-to-head comparisons, we conducted indirect comparisons using statistical techniques to estimate the treatment effects from studies of each given treatment against controls under an assumption of consistency. We used adjusted indirect frequentist comparisons. To address the problems with inevitable differences across studies we used mixed (or multiple) treatment comparisons (MTCs), sometimes called network meta-analysis. Network meta-analysis refers to methods that compare treatments by combining all available evidence from studies that form a network of evidence (including

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			studies comparing three or more treatment arms) in the absence of direct head-to-head comparisons. By synthesizing direct and indirect comparisons, we improved the precision of estimates for treatment effects. A Bayesian analysis can construct complicated models with fewer assumptions and permits explicit posterior inference regarding the probability that each treatment is "best" for a specific outcome. We calculated Bayesian odds ratios with 95 percent credible intervals and Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments. We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class did not demonstrate significant differences in outcomes. All Bayesian results were obtained from the Win BUGS software; using Markov chain Monte Carlo (MCMC) samples after a 50000-sample algorithm burn-in.
Reviewer 2	**Comments for statistical methods for adults section**	For studies without events in both arms, we don't recommend to include them in the meta-analysis.	We revised the report clarifying pooling criteria

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Reviewer 2	**Comments for statistical methods for adults section**	Similar, for indirect comparison, why are both Baysian network meta-analysis and indirect adjusted frequestist analysis needed? What is the justification to use one in one analysis and use another in a different analysis? Also it is not clear whether they checked the consistency within the network in their analysis	We clarified that used we used adjusted indirect frequentist comparisons for individual drugs that were compared to placebo. To address the problems with inevitable differences across studies, we used mixed (or multiple) treatment comparisons (MTCs), or so called network meta-analysis. Network meta-analysis refers to methods that compare treatments by combining all available evidence from studies that form a network of evidence (including studies comparing three or more treatment arms) in the absence of direct head-to-head comparisons. By synthesizing direct and indirect comparisons, we improved the precision of estimates for treatment effects. A Bayesian analysis can easily construct complicated models with less assumptions and permits explicit posterior inference regarding the probability that each treatment is "best" for a specific outcome. We calculated Bayesian odds ratios with 95 percent credible intervals and Bayesian network random effects meta-analysis assuming heterogeneous variances across treatments. We synthesized evidence from drug classes in network meta-analysis when individual drugs from the same class did not demonstrate significant differences in outcomes. All Bayesian results were obtained from the Win BUGS software, using Markov chain Monte Carlo (MCMC) samples after a 50000-sample algorithm burn-in
Reviewer 2	**Comments for statistical methods for adults section**	Then in some tables, three measures, Cohen SMD, and mean difference and mean ratios were used. Mean ratio was not mentioned in the methods section, and it is not clear what is the purpose to report all three measures.	We revised the report and clarified that for continuous outcomes we calculated the mean differences from the reported means and standard deviations. We also calculated ratios of means that describe clinically interpretable percentage differences in outcomes with active versus control drug interventions. We calculated standardized mean differences for different measures of the same outcome with Cohen and Hedges methods.

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Reviewer 2	**Comments for statistical methods for adults section**	Specify explicitly how the missing data were handled or imputed in the intention to treat analysis. What correction coefficients were used in what conditions?	We clarified that we used default correction coefficient available in STATA and Meta-analyst. We enforced intention to treat analysis for all calculations using the number of randomized subjects into trial arms.
Reviewer 2	**Comments for statistical methods for adults section**	All estimates reported 95% CI, but it is not appropriate to say that "at a 96 percent confidence level, we calculated … " or similar.	We deleted this sentence.
Reviewer 2	**Comments for statistical methods for adults section**	Specify the type of standardized mean difference used in the analysis.	We used Cohen SMD for concluding treatment effects.
Reviewer 2	**Comments for statistical methods for adults section**	No results on meta-regression and sensitivity analysis were mentioned in the text.	We provided the results from meta-regression in the table "Adverse effects with onabotulinumtoxin A vs. placebo meta-regression by study level factors."
Reviewer 2	**Comments for statistical methods for adults section**	No results on heterogeneity were mentioned in the text. The CER did not provide any forest plot. In some tables, the results from the individual studies were provided. In many other cases, it is hard to evaluate how consistent the results were among studies. It would still be helpful to provide forest plots, at least for important results.	We added the results from the statistical tests for heterogeneity in the tables with pooled analyses. We provide 2 forest plots reporting the results from network Bayesian meta-analysis.
Reviewer 2	**Comments for statistical methods for adults section**	In some tables, for example, table D17, only one number is reported for 95% CI.	We revised the tables always reporting 95%CI.

Commentator & Affiliation	Section	Comment	Response
Reviewer 2	**Comments for statistical methods for children section**	The general statistical framework is similar to that of the children section without indirect or network analysis. Therefore all above comments for adults section, except for the one related to indirect or network analysis, apply to this section. The general statistical framework is fine. Here are some comments for the investigators to consider: One general question is that usually multiple methods are specified for the same situation; however, it is not clear which method was used in the analysis, why the multiple methods are needed and what are the criteria for the choice of methods. For example, for spare data, fixed effects MH RR, and Peto OR, double arcsine transformation and RE generalized nonlinear mixed effect models are mentioned. Why all these methods are needed? It is not clear which method is used for which condition. I don't see results from OR and double arcsine transformation in the text either about comparison between two treatments. The investigators may just pick one appropriate methods and stick with it. If there is the need to use alternative method, please provide justification. And then why a Bayesian OR is needed? The investigators added 2% as the cutoff point to use fixed effects MH RR, and Peto OR, but it is still not clear which measure was used. The results section do not seem to have results based on Peto OR.	We clarified that:"For continuous outcomes we calculated mean difference and standardized mean differences for different continuous measures of the same outcome. To address clinical importance of the changes in continuous outcomes we also calculated means ratio. The means ratios clarified clinical interpretations of the differences in means. We provide mean ratios with 95%CI in appendix tables." We clarified that "we synthesized sparse data (defined as rates less than 2 percent) on adverse effects of the drugs using Peto odds ratio, and arcsine transformed absolute risk. We evaluated robustness of adverse effects estimates comparing the results from described statistical models." We provided Peto odds ratios and arcsine transformed mean differences. We reported the differences in the results from the described statistical models as follows:" "Viral infections were more common with larger doses of divalproex according to the arcsine transformed risk difference that reached statistical significance". We provide heterogeneity statistics for all pooled analyses.
Reviewer 2	**Comments for statistical methods for children section**	In addition, what does it mean "we used a logarithmic scale to analyze the adjusted regression coefficient with a standard error of association between treatments and patient centered outcomes."?	We clarified this sentence as follows: "We analyzed adjusted relative risk from observational studies that examined the association between treatments and patient-centered outcomes."
Reviewer 3	**Quality of the Report**	Poor	We revised the report following your recommendations, which will improve the quality of the report.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**General Comments**	1.I am truly beside myself on how bad this review is. Let's start with just the utter nonsense of repeating whole sections of the paper multiple times. What for? 2. Next is references, how many times and variations of references can one list in a single review. They don't even make sense from a section of the paper. 3. Third grammar is even worse than mine. 4. Fourth, there is a clear and distinct demonstration of a lack of clinical understanding of migraine and migraine trials.	1. The structure of the evidence-based reports always includes the executive summary with the most important findings and key messages and the report with detailed and transparent information about all available and analyzed evidence. The executive summaries are posted on line in the AHRQ website with links to the full reports. 2. We provided separate lists of the references for 2 executive summaries (children and adult), 2 reports, and for each appendix following the editorial requirements from the AHRQ. 3. We revised the report to improve the clarity of the writing. 4. We developed the protocol following analytical framework proposed by the International Headache Society. We used the definitions of migraine recommended in 2005 by the Headache Classification Subcommittee of the International Headache Society. Since migraine preventive drugs had been approved by the FDA before 2005 we opted analyzing the evidence from all migraine prevention trials that had been conducted before 2005. We evaluated methodology of the trials following the Subcommittee on Clinical Trial of the International Headache Society. We are not aware of any migraine specific FDA recommendations for good clinical practice in drug evaluation.
Reviewer 3	**Introduction**	1.Definitions are wrong (two different chronic migraines? not likely), dated (pediatric), lack of understanding of migraine literature so missed at the least 50 DB-PC RCT by my estimate. 2. Additionally there are numerous trials that were excluded for reasons that are unwarranted, for example why exclude flunarizine but mention dotarizine and cinnarizine? none in the US and why exlcude a drug from out of fda approval but include unlableled use and even then to do so selectively for example histamine. or how about tonnabersat which	1. We used the definitions of migraine according to the most recent HIS guidelines. We conducted a comprehensive literature search in several databases as well as manual search of the reference lists of the textbooks, guidelines, reviews, and all eligible studies. We hope that published guidelines and expert recommendations would mention all relevant migraine prevention studies. We also analyzed availability of the results from the NIH funded studies and registered trials. We added in the discussion section that

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		was never even submitted to the fda for review.	despite all our efforts we do not know how many relevant studies we missed. We believe that our findings of limited availability of studies with poor results have implications for clinical research policy. We propose that all trials should be registered and all results should be available for the public and independent researchers. 2. We did review flunarizine studies but did not rank the strength of evidence for this drug because it has not been approved by the FDA. We did not review notarizing, which is not available in the US. We did not review injections of histamine. We clarified that we developed a list of eligible drugs according to the discussion with key informants, the TEP members, and the public comments. We did review off-label drugs available in the US. We do not have knowledge about ongoing FDA reviews. We clarified that during the topic refinement stage, we solicited input from Key Informants representing medical professional societies/clinicians in the areas of neurology, primary care, consumers, scientific experts, and payers, to help define the Key Questions (KQs). The KQs were then posted for public comment for 4 weeks from April 12, 2012 to May 10, 2012, and the comments received were considered in the development of the research protocol. We next convened a Technical Expert Panel (TEP) comprising clinical, content, and methodological experts to provide input in defining populations, interventions, comparisons, and outcomes, and in identifying particular studies or databases to search. The Key Informants and members of the TEP were required to disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts. Any potential conflicts of interest were balanced or mitigated. Neither

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			Key Informants nor members of the TEP performed analysis of any kind, nor did any of them contribute to the writing of this report. Members of the TEP were invited to provide feedback on an initial draft of the review protocol which was then refined based on their input, reviewed by AHRQ, and posted for public access at the AHRQ Effective Health Care Website.
Reviewer 3	**Methods**	1.reporting tables are so confusing and inconsistent that they can't even be used to assess the writing for the most part. 2.The statistics are as has been said of them, a tool to prove whatever you want. How can one possibly justify candesartan with a total of 12 patients enrolled in one study as being better and safer than the FDA approved drugs alone or collectively. and that is just the start. 3.An independent statistician who is experienced in migraine studies needs to be hired to perform independent review of stats as well as the methodology chosen.	1. All tables have very similar format to provide reproducible estimation of the treatment effects and evaluation of the strength of the evidence. 2. We used statistical methods recommended in the guidelines for systematic literature review of health care interventions. We focused on the best evidence from head to head RCTs. Clinicians indirectly compare the effects of the drugs just by reading the articles that report rates of the outcomes with different drugs. All we did with indirect comparison was providing actual statistical estimates of comparative effectiveness based on published literature. Bayesian net work meta-analysis if being used by the FDA for policy decisions. The large number of off label drugs may reflects the fact that approved drugs have undesirable balance between benefits and harms. We revised the report clarifying the exploratory nature of the conducted indirect comparisons. Candesartan was examined in one RCT of 60 patients aged 18 to 65 years. 3. We did consult independent statistical researchers with expertise in trial meta-analyses and network meta-analyses. All researchers do not have COI. We are not aware of any migraine specific analytical recommendations from the FDA or the HIS guidelines.

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Reviewer 3	**Results**	1.their are numerous errors with studies being excluded when they shouldn't, miss classified to entirely wrong areas. 2.let alone things like wrong drug classifications. 3.whatever came of strength of evidence? 4.whatever became of basic math. you report over 700 patients in trials of antidepressants where ever did you get those numbers from? I can't make it add from any of your tables collectively. 5. And did anyone actually read the papers as you got caught in the famous two reports of the same research by two different coauthors on at least one report.	1. We rechecked all excluded studies to make sure that migraine prevention trials were analyzed. The table you commented on as misclassification provided a comparison of baseline subjects' characteristics in the trials that examined different drug classes. For example, the trials of ACE inhibiting drugs (a column with Active treatment) were compared with propranolol (a column with control treatment). It does not mean that we classify propranolol as an ACE inhibitor. We revised this table to avoid confusion. 2. We used the WHO drug classification system that does not include tonabersat. We corrected the drug class for this medication following your recommendations. 3. We provide ranking of all SOE domains according the AHRQ guideline. 4. We revised the table for simple tracking of the number of the subjects in the trials. 5. We are not sure we know "the famous reports" you mention.
Reviewer 3	**Discussion/ Conclusion**	Since there are so many issues with the rest of this and since the authors repeatedly demonstrated little to no understanding of migraine the rest of the discussion, conclusion future research area are nearly meaningless., since they are based on a variety of errors.	We believe that we have provided comprehensive reproducible and transparent evidence synthesis following the known good practice in clinical research recommendations.
Reviewer 3	**Clarity and Usability**	this is the worst written report I have ever seen. 700 pages of repeated whole sections, undecipherable tables. poor referencing.	We revised the report following your specific comments wherever feasible.
Reviewer 3	**ES: Chronic migraine affects 8 to13 percent of adults**	this is the percentage for episodic migraine not chronic migraine which is the 1 to 3 % range	We revised this sentence according to the recently published systematic review of the prevalence of chronic migraine that stated: "The prevalence of CM was 0-5.1%, with estimates typically in the range of 1.4-2.2%. Seven studies used Silberstein-Lipton criteria (or equivalent), with prevalence ranging from 0.9% to 5.1%. Three estimates used migraine that occurred ≥15 days per month, with prevalence ranging from 0 to 0.7%."

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Reviewer 3	**ES: Forty percent of people who experience episodic migraines might benefit from preventive medication;3, 12, 13 yet, only about 12 percent of adults with frequent migraines take preventive medication.2, 3, 12, 13**	these all reference the same data set	We revised the reference list keeping the most updated unique publications.
Reviewer 3	**ES: For prevention of chronic migraine, the FDA has approved only one drug, botulinum toxin.**	only onabotulinumtoxin a. the other toxins are not approved	We revised this sentence as follows: "For prevention of *chronic* migraine, the FDA has approved only one drug, onabotulinumtoxin." We clarified that we used the WHO drug classification system that categorizes botulinum toxins under one category-M03AX01. The U.S. Food and Drug Administration approved Botox injection (onabotulinumtoxin A) for chronic migraine. Botulinum neurotoxin type A (marketed as BoNT-A; BOTOX, Allergan Inc.) was examined in several RCTs. Two RCTs examined Abobotulinumtoxin A (marketed as Dysport). We did not detect statistically significant differences in outcomes among botulinum formulations.
Reviewer 3	**ES: Treatment safety is defined by the rates of adverse effects that lead to treatment discontinuation.**	not true, it also includes all AE reports	We revised this sentence as follows: "Treatment safety is defined by the total rates of adverse effects and adverse effects that lead to treatment discontinuation."
Reviewer 3	**ES: The American Migraine Prevalence and Prevention guideline recommends preventive treatment for those with two or more headache days with disability or four or more days with or without disability.[30]**	this was a paper based on the data from the AMPP, it was not a guideline it is a recommendation based on expert opinion (mine was one of those)	We revised this sentence as follows: "The American Migraine Prevalence and Prevention expert advisory group recommends preventive treatment for those with two or more monthly headache attacks with disability or four or more monthly attacks with or without disability."[30]
Reviewer 3	**ES: What are the harms from preventive pharmacologic treatments when compared to placebo or no active treatment?**	i am just waiting to see how you deduce the no active treatment harms. and even how you define it since the burden of migraine on qol, economics etc are certainly harms that are not benefited by no active treatment	Adverse effects rate in persons receiving placebos is a standard way to identify attributable harms. We found no studies that examined treatment utilization for adverse effects with drugs.

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Reviewer 3	**ES: We searched several databases including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database to find original studies published in English up to March 29, 2012.**	there is a wealth of DBPC RCT that were published in books (peer reviewed) as well as at least one journal that was not in medline that published similar process. you missed all of these.	We clarified that we indeed manually searched the references in the textbooks, published guidelines, reviews, and all eligible studies to find relevant trials. We also provided the results availability analysis of the NIH funded and registered in several trial registries. We clarified in the discussion that despite all our efforts in finding relevant studies we still do not know how many relevant trials we missed. We added that our findings have implications for research policy suggesting that all human experiments should be registered and the results should be available for the independent researchers and the general public.
Reviewer 3	**ES: Eligible studies included patients with … chronic daily headache, … defined according to the criteria of the International Headache Society.24**	this should not have been examined as it is not migraine	The FDA approved several drugs before the most recent definition of migraine was published. After analyzing the FDA documents and discussion with the TEP we opted to include the trials that defined chronic daily headache following migraine diagnostic criteria.
Reviewer 3	**ES: We also excluded studies of short-term prevention of migraine, including menstrual migraines.**	you also excluded drugs that were not fda approved here but elsewhere such as flunarizine. but you included doatarizine	We did not include the studies of dotarizine because it is not available in the US. We examined but did not rank strength of evidence from the studies of flunarizine since this drug is not available in the US.
Reviewer 3	**ES: Subheading: Risk of Bias Assessment**	how many times do you use these same paragraphs in this document? what a waste.	We present our findings according to the recommendations from the AHRQ guideline.
Reviewer 3	**ES: FDA approved four drugs for prevention of episodic migraine based on trials conducted prior to the recent implementation of the migraine definition proposed by the International Headache Societ.**	5 you missed sansert	We did review this drug. However, sansert (METHYSERGIDE MALEATE) was discontinued according to the FDA website.
Reviewer 3	**ES: Few trials reported the proportion of obese subjects,**	until a few years ago this was on no radar screen. if you want to cite this you should be citing a variety of other comorbidities.	We pointed out that very few studies reported the proportion of the patients with specific comorbidities.

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Reviewer 3	**ES: …one approved drug for chronic migraine (botulinum toxin)…**	failure to differntiate from other toxins	We clarified that only onabotulinumtoxin was the FDA approved for chronic migraine. We clarified that we used the WHO drug classification system that categorizes botulinum toxins under one category-M03AX01. The U.S. Food and Drug Administration approved Botox injection (onabotulinumtoxin A) for chronic migraine. Botulinum neurotoxin type A (marketed as BoNT-A; BOTOX, Allergan Inc.) was examined in several RCTs. Two RCTs examined Abobotulinumtoxin A (marketed as Dysport). We did not detect statistically significant differences in outcomes among botulinum formulations.
Reviewer 3	**ES: Botulinum toxin was better than placebo in reducing monthly migraine attack by ≥50 percent**	only onabotulinum toxin a.	We revised the report clarifying the exact type of botulinum toxin.
	off-label beta blockers… were better than placebo in reducing monthly migraine frequency by ≥50 percent in individual patients	not all of them	We revised the report providing the effects of the specific beta-blockers on reducing monthly migraine by ≥50 percent in individual patients.
Reviewer 3	**ES: Only one off-label drug, captopril, resulted in more than 500 patients showing clinical response**	wild claim for a bad study	We revised the report clarifying that limited evidence from a single RCTs demonstrated that off-label drug, captopril, resulted in an attributable clinical response in more than 500 patients per 1,000 treated.
Reviewer 3	**ES: Beta blockers metoprolol, atenolol, and nadolol but not pindolol were better than placebo in markedly reducing migraine attacks**	contradicts your statement 3 paragaphs up.	We revised the report clarifying the evidence from efficacy RCTs of individual drugs and from network meta-analysis of approved drugs vs. off label dug classes.
Reviewer 3	**ES: Antidepressants … tonabersat**	not an antidepressant	We used the WHO drug classification system that does not include tonabersat. We revised the report using the Medline classification of this drug as “Cortical spreading depression inhibitor.”

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Reviewer 3	**ES: Indirect adjusted frequentist analysis demonstrated that the angiotensin II receptor antagonist candesartan was more effective than topiramate, propranolol, timolol, valproate, metoprolol, gabapentin, and amitriptyline.**	what a piece of garbage show you can do anything iwth stats. but i am dubious overall of bias by this writing group. independent stats will be needed for review of all stats as well as methodology chosen.	We used well-recognized statistical methods for direct, indirect frequentist, and Bayesian network meta-analyses that are recommended by the Cochrane collaboration, the AHRQ guidelines, or the International Society for Pharmacoeconomics and Outcomes Research Indirect Treatment Comparisons Good Research Practices Task Force. Such methods have been published in peer reviewed core clinical journals. Independent and free of COI statisticians reviewed the methods and the results.
Reviewer 3	**ES: Patients experienced eyelid edema with 50U of botulinum toxin more often than with 7.5 or 25U.**	never used this dose it was 75u	BoNTA-024-026-036 Study Group randomized patients to treatment with placebo or BoNTA (7.5 U, 25 U, or 50 U), PubMed ID: 17018329
Reviewer 3	**ES: Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal, dry mouth, marked anorexia, paresthesia or fatigue, mood problems, nausea, and weight loss.**	anyone proof your writing? don't think so.	We revised this sentence as follows: “Larger doses of topiramate caused higher risk of anorexia, depression, paresthesia, and difficulty in memory leading to treatment withdrawal. Larger doses of topiramate caused higher risk dry mouth, paresthesia or fatigue, mood problems, nausea, and weight loss.”
Reviewer 3	**ES: Botulinum toxin decreased the likelihood of acute drug use in patients with a baseline of more than 12 monthly migraine days (RR 0.78, 95 percent CI, 0.66 to 0.92).**	site your references. throughout.	We did include all references in the report. We have provided not more than 50 references in the executive summary following the ARHQ recommendations.
Reviewer 3	**ES: Subheading: Concurrent Prophylactic Medication**	what a stupid paragraph. what is this suppose to prove?	Concurrent medications could modify the effects of the examined in RCT migraine preventive drugs. The original RCTs justified reported subgroup analyses. Existing guidelines recommend examining the role of concomitant treatments in systematic reviews of health care interventions.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**ES: Topiramate caused a complete cessation of migraine attacks in women but not in men according to a low risk of bias RCT.**	site your reference	We provide all references in the report and appendices. The executive summary has restricted reference number.
Reviewer 3	**ES: Subheading: presence of aura**	topriamate was more effective in mwa than moa. my paper, johns hopkins journal you have it cited in peds in wrong section	We revised this paragraph clarifying that post hoc analysis of one RCTs demonstrated that topiramate was better than placebo in reducing the number of migraine attacks in subjects with aura. The drugs were not better than placebo in planned intention to treat analysis of all randomized patients. The trial you conducted reported the results in patient with aura only (CN-00474164). We revised the report reporting the results from this trial.
Reviewer 3	**ES: However, topiramate, divalproex, and off-label antiepileptics and antidepressants resulted in bothersome adverse effects leading to treatment discontinuation more often than placebo.**	1.you missed sanert, histamine cyproheptadine, nsaids mini prevention with triptns, which you should have included. 2. never looked at menstrual migraine, why not?	1. We focused on the drugs available in the US. We did review preventive effects with NSAIDs. 2. Short term migraine prevention and prevention of menstrual migraine was beyond our scope which was formulated after public comments and discussions with the TEP.
Reviewer 3	**ES: Only one off-label drug, captopril, resulted in an attributable clinical response in more than 500 patients per 1,000 treated**	but look at the extrapolation you have to make for this drug from its one study!	We revised the report emphasizing that one RCT reported a large preventive effect with captopril. Future research should examine comparative effectiveness of off label angiotensin inhibiting drugs and beta-blockers for migraine prevention.
Reviewer 3	**Report, results: We estimated that investigators had to screen about two patients to enroll one subject in RCTs of antiepileptic drugs or angiotensin II antagonists, three patients to enroll one subject in RCTs that examined beta blockers, and four patients to enroll one subject in RCTs of antidepressants**	how did you estimate this? having done trial for 25 years your numbers are almost backwards from reality. and actually are more dependent on when trial was done than anything else.	We calculated the number needed to screen from the reported number of screened, eligible, enrolled, and randomized patients. We agree that our estimations were based on rarely reported information and have poor applicability so we deleted them.

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Reviewer 3	**Report: Studies examined four approved drugs for episodic migraine (topiramate, divalproex, propranolol, and timolol),.. one approved drug for chronic migraine**	1.should have report ed on the migraine trials with botxi ina ddtion to the crhonc migraine trials 2. you also mixed thing up by reporting topamax trials fro CM as for epsidoc migraine.	We revised this section adding the effects of topiramate on chronic migraine. We also added a recently published trial that examined adding propranolol to topiramate treatment in adults with chronic migraine who failed topiramate monotherapy.
Reviewer 3	**Report: Topiramate was also better than placebo in reducing monthly migraine days by ≥50 percent (high strength of evidence**	missed mwa vs moa trial	The trial you mentioned did not compare topiramate effects in adults with vs. without migraine. Post hoc subgroup analysis reported statistically significant reduction in migraine attacks only in patients with aura.
Reviewer 3	**Report: Improvement in disability was large and clinically important in adults with chronic migraine according to the RCT from the TOPMAT-MIG-201 (TOP-CHROME) Study Group (Appendix Table 26).88**	clsassifed in wrong section	We moved this sentence to the section about prevention of chronic migraine.
Reviewer 3	**Results: Trials enrolled 2,687 adolescents and adults with episodic migraine.**	where did you ever get that number. I can't come within a power of 10 from your data.	We added the tables with the numbers of the enrolled for each drug class.
Reviewer 3	**Results: Topiramate caused a complete cessation of migraine attacks and a reduction of monthly migraine attacks by 50 percent in women but not men according to one low risk of bias RCT.186 Topiramate caused a complete cessation of migraine attacks in 37 (95 percent CI, 8 to 67) and a reduction of monthly migraine attacks by 50 percent in 249 (95 percent CI, 178 to 320) per 1,000 treated women.186**	but what about the other trials.	We found no trials that reported drug effects in gender subgroups.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children report, Executive Summary**	what is suppose to be the difference between this and following section? for many of what would be comments here look in next section	We present the data based on the AHRQ requirements for the evidence based reports. The posted on line executive summary provides concise summary statements. The reports provide detailed description of the methods and the results.
Reviewer 3	**Children Report, Executive summary: We retrieved 507 references, excluded 349 references, and included 22 references for 21 RCTs and 40 publications of nonrandomized studies**	this is a very biaed statement in istelf sicne a cursory rveiw of the exclued studies reveals that almost none of them have anything to do with pediatric headache. It should also be noted that again on just cursory reveiw there are at least 3…at least 3 clincial trials that are excluede that are RCT in migraine (which we cited in the just published guidelines from aan and ahs.	We revised the study flow and clarified in the text exclusion at screening not relevant to pediatric migraine studies. We reviewed reference lists of the recently published guidelines for episodic migraine prevention in adults to confirm inclusion of all relevant children studies.
Reviewer 3	**Children Report, the Executive Summary: The antiepileptic drugs clonidine, trazodone, and magnesium oxide failed to prevent migraine in children.**	the drugs lists are AEDs sloppy writing	We revised these sentences in the executive summary correcting appropriate drug classes as follows:"The antiepileptic drugs, clonidine, trazodone, and magnesium oxide failed to prevent migraine in children. Moreover, two antiepileptic drugs, topiramate and divalproex sodium, both resulted in treatment discontinuation due to adverse effects." We revised these sentences in the report correcting appropriate drug classes as follows: "The antiepileptic drugs, clonidine, trazodone, and magnesium oxide failed to prevent migraine in children. Antiepileptic drugs topiramate and divalproex sodium not only failed to benefit children with migraine but also resulted in treatment discontinuation due to adverse effects."
Reviewer 3	**Children report, the Executive Summary, Discussion: "Moreover, two other antiepileptic drugs, topiramate and divalproex sodium, both resulted in treatment discontinuation due to adverse effects** "	biased writing peopel d/c drgus in all the studies not just these	We clarified that both drugs increased a risk of intolerable adverse effects leading to treatment discontinuation when compared to placebo as follows:"The increase in the rates of intolerable adverse effects resulted in treatment discontinuation was statistically significant with both drugs."

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Executive summary: Few clinical trials followed the recommendations from the Task Force on Adverse Events in Migraine Trials of the International Headache Society86 when examining the potential harms of these drugs when used in children**	that's because most were done before the guidances were published.	We revised the report pointing out the importance of appropriate design in determining safety of the drugs for children with migraine as follows: "Future fully powered trials involving children with migraine should examined long term safety with preventive drugs irrespective of investigators' perception about the causality of the drugs on detected harms."
Reviewer 3	**Children Report, Executive summary: On average, the trials lasted 20 weeks and therefore did not provide sufficiently long-term evidence for the benefits and harms of drugs that could be recommended for preventive use over very long periods.**	long time for clinical trials in migraine	Available publications do not specify recommended duration of preventive treatments. Pediatric safety trials should examine adverse effects at 12 months or more. Long-term harms can be detected at years of followup. We revised the report clarifying that, "The duration of preventive treatment and sustained benefits and harms with preventive drugs in children with migraine remain unclear."
Reviewer 3	**Children Report, Executive summary: Our comprehensive literature search of several databases, trial registries, and the FDA reviews detected a very low publication rate of registered completed clinical trials involving children.**	if you don't even know the field how could you even make such ludicrous statements. you have no idea as to the why so instead you make some ignorant remark.	Our goal was a comprehensive analysis of evidence. We found that many studies involving children with migraine have never been published. We clarified that we could not know why the studies were not published. We added a section about poor availability of the results from clinical studies involving children with migraine: "Our report has clinical research policy implications. Existing clinical research policy does not guarantee availability of the results from all studies involving children. Results are unavailable for more than half of the studies involving children, revealing a substantial publication bias. Registration and posting of results on ClinicalTrials.gov should be mandatory for all studies involving children."

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Introduction:** Childhood migraine is more prevalent in lower income families. Among adolescents, migraine is more prevalent in whites than African Americans. According to the International Classification of Headache Disorders (ICHDII), migraine is a common disabling primary headache disorder anifesting in attacks that last from 4 to 72 hours.	these are strong statements based on a single study; classification for pediatric headache was updated years ago. this is antiquated	We clarified that this data came from the largest population based cohort in the US. We revised the report as follows: "The American Migraine Prevalence and Prevention study of 32,015 adolescents found that childhood migraine is more prevalent in lower income families. The same study reported that among adolescents, migraine is more prevalent in whites than African Americans." We used the classification from the Headache Classification Subcommittee of the International Headache Society, 2004. The www.i-h-s.org website and the most recent publications in Pediatrics in 2009 (PubMed Id 19289227) cited the same classification from 2004. We added a definition of pediatric migraine with and without aura in Appendix C
Reviewer 3	**Children Report, Introduction: Among adolescents, migraine is more prevalent in whites than African Americans.**	duplicate	We deleted this duplication.
Reviewer 3	**Children Report, Introduction: Chronic migraine affects 2 percent of children and adolescents.**	definitions and with this percantages are being mixed. this is so wrong	We revised this section about prevalence of migraine in boy and girls, prevalence of episodic migraine with and without aura, and prevalence of chronic migraine.
Reviewer 3	**Children Report, Introduction: Migraine significantly affects children's physical, psychological, and social well-being and can impose serious lifestyle restrictions.**	where are these references your system is impossile to follow.	We added a table with prevalence of chronic migraine from the Chronic Daily Headache in Adolescents Study (C-dAS) with the references.
Reviewer 3	**Children Report, Methods: We specifically opted not to synthesize studies of flunarizine because the FDA has not approved it.**	but it is approved around the rest of the world and you have no idea why it was never approved. I do.	We added in the discussion section that:"We do not know why this drug was never approved in the US. We requested the FDA review of this drug. We received a response that :" Any information on an application if submitted by a firm to the FDA that did not yet receive approval, belongs to the manufacturer/sponsor developing the drug (21 CFR 314.430)" We did not contact the sponsors directly to inquire about products under development."

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Methods: We searched for published studies in several databases, including MEDLINE® (via Ovid and PubMed®), the Cochrane Library, and the SCIRUS bibliographic database**	you missed peer reviewed studies published from the migraine trsut as well as from non medline sources.	We did review the reference lists of the identified guidelines, textbooks, and systematic reviews to find all relevant studies.
Reviewer 3	**Children Report, Methods: Three investigators independently determined study eligibility according to recommendations from the Cochrane Handbook for Systematic Reviews of Interventions.36**	why did you not reference IHC guidances on clinical trials in headache. Nor previous guidelines examining these issues?	In conducting systematic reviews of the literature we follow the AHRQ *Methods Guide and the Cochrane Handbook for Systematic Reviews of Interventions. We* developed the protocol and PICOT criteria based on the Headache Classification Committee of the International Headache Society and the IHC methodological guidelines.
Reviewer 3	**Children Report, Methods: Target population of community-dwelling children with episodic migraine, chronic daily headache, or chronic migraine defined according to International Headache Society criteria for chronic migraine.**	chronic daily headache is not even in the IhC classification	To synthesize the evidence from the trials published before the most recent International Headache Society diagnostic criteria of migraine, we include the trials with previously used chronic daily headache definitions.
Reviewer 3	**Children Report, Results: The trials included 1,125 children ages 9 to14. Sample size of RCTs averaged 112.5±109 children, with boys constituting 51 percent.**	reconcile this with statements above about percentage female	We revised the report providing all numbers in the tables.
Reviewer 3	**Children Report, Results: RCTs had low risk of bias, with double-blind design and low risk of bias in eight of 10 trials (Appendix Table D8).**	which and how many studies used which definitions for defining migraine and which recommended research protocols.	We added a table with this information.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Results: Absolute reduction in migraine days with topiramate, 50 to 200 mg/day, was not better than with placebo in pooled analysis of two double-blind RCTs.**	dose relationship	We report dose response association with outcomes from all trials that examined it and provided reproducible results. We added tables with dose response association with adverse drug effects in children.
Reviewer 3	**Children Report, Results: A single small double-blind crossover RCT examined the efficacy of trazodone versus placebo.**	these are the same study. what a stupid way of presenting the data	We reported that it was a single RCT indeed. We present the results according to the guidelines for systematic reviews of health care interventions:"We present the findings providing the reproducible statistical estimates of treatment effects and strength of evidence evaluation."
Reviewer 3	**Children Report, Results: We estimated that 713 children per 1,000 treated would have no migraine attacks with propranolol.5**	how can you get this number with 14% of kids having "cessation"of migraine. whatever that is and it was no different from DVA which you panned above	85% vs. 14% children with drug vs. placebo respectively reported no migraine attacks at 26 weeks after randomization. Then absolute risk difference is 0.713 or 71%. The number of attributable events per 1000 treated is 1000* absolute risk difference or 713. We clarified in the abstract and in the methods section that "We calculated absolute risk differences and pooled them with random-effects models, and calculated numbers of outcome events attributable-to-treatment effects per 1,000 treated as absolute risk difference multiplied by 1000. " "The number of avoided or excess events (respectively) per population of 1,000 is the difference between the two events rates multiplied by 1,000".

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Results: How do preventive pharmacological treatments affect patient-centered and intermediate outcomes when compared to active pharmacological treatments?**	comparator trials without a placebo are of limited predicitive quality	Placebo controlled randomized clinical trials provide the evidence of efficacy of the drugs. Comparative effectiveness randomized controlled clinical trials answer the questions which drugs are more effective and save. Comparative effectiveness trials should examine the drugs that had been shown efficacy (better than placebo). We added information about development of comparative effectiveness questions after considering public comments (the questions were posted in the AHRQ website for 1 month) and discussions with key informants and the Technical Expert panel. **Topic Refinement and Review Protocol** After discussion with key informants and the Technical Experts Panel, we formulated research questions and a list of eligible pharmacological classes.
Reviewer 3	**Children Report, Results: Limited evidence from individual RCTs suggested no differences in migraine prevention with examined drugs including propranolol, valproate, and topiramate.**	this conflicts iwth statemnts above	We clarified that this sentence concluded no differences in comparative effectiveness studies.
Reviewer 3	**Children Report, Results: Topiramate A higher dose of topiramate compared to a lower dose (100 versus 25 mg) demonstrated no consistent significant difference in migraine prevention.**	this is one of the most convoluted ways of presenting data I have ever seen.	We clarified that “The evidence did not support a dose-response association between increased doses of topiramate and reduction in migraine frequency or disability”.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Report, Results: Multidisciplinary drug management including cognitive-behavioral training was more effective than usual care combined with an educational intervention in preventing migraine in children and adolescents (one RCT of 68 children, low strength of evidence).**	very stong statement based on low eveidnece small trials	We downgraded strength of evidence from a single small RCT to low due to imprecise treatment estimate and unclear risk of bias.
Reviewer 3	**Children Report, Results: One small nonrandomized study demonstrated that 8 percent of adolescents treated with botox 100U every 3 months experienced blurred vision and ptosis, and burning sensations at all injection sites (Appendix Table D48).**	safety but no efficacy report. to what purpose?	We reviewed RCTs and controlled clinical trials for drugs efficacy and comparative effectiveness. We reviewed all evidence of adverse effects with drugs. We could not find RCTs or controlled clinical trials of botox efficacy in children. We found one uncontrolled case series that examined outcomes after botox treatments. We report the rates of adverse effects with this drug since the study design did not meet our threshold for evident benefits.
Reviewer 3	**Adult Appendix Table D11. Differences in subject characteristics in randomized controlled clinical trials that examined drugs for migraine prevention in adults**	many of these drugs are misclassified	This table provided differences in patient characteristics across the trials (indirect comparison at trial level). The subheadings point out that the column with active and the column with control drugs report the drugs from different classes. We revised this table to avoid confusion.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Adult Appendix Table 12. Randomized controlled clinical trials that examined efficacy of botulinum toxin for migraine prevention in adults**	dysport and botox are not equivalent	We marked the trials of dysport (2 references). We did not detect statistically significant differences in outcomes among botulinum toxin formulations. No trials directly compared Onabotulinumtoxin A (marketed as Botox) with Abobotulinumtoxin A (marketed as Dysport). We clarified that we used the WHO drug classification system that categorizes botulinum toxins under one category-M03AX01. The U.S. Food and Drug Administration approved Botox injection (onabotulinumtoxin A) for chronic migraine. Botulinum neurotoxin type A (marketed as BoNT-A; BOTOX, Allergan Inc.) was examined in several RCTs. Two RCTs examined Abobotulinumtoxin A (marketed as Dysport). We did not detect statistically significant differences in the reported outcomes among botulinum formulations.
Reviewer 3	**Adult Appendix Table D16. Decrease in migraine frequency of at least 50% with botox, pooled results from randomized controlled clinical trials, random effects models with inverse variance weights**	nothing like combining highly dissilmar studies into one pool!	Our pooled analyses did not show differences in the outcomes among botulinum formulations. We marked the trials of disport. Future research should demonstrated that dysport and botox are not equivalent.
Reviewer 3	**Adult Appendix Table D17. Migraine headache frequency (change from baseline) with botox, pooled results from randomized controlled clinical trials, random effects models**	the dose was not 7.5 u it was 75 units	BoNTA-024-026-036 Study Group randomized patients to treatment with placebo or BoNTA (7.5 U, 25 U, or 50 U), PubMed ID: 17018329

Commentator & Affiliation	Section	Comment	Response
	Appendix Table 127. Funding and conflict of interest in randomized controlled clinical trials that examined adverse effects with topiramate versus placebo	how do you rationalize this obviously problematic reporting of COI for any given investigator?	Previous research demonstrated that industry sponsored trials demonstrated favorable effects of the examined treatments. Consistent and transparent reporting of t COI is mandatory in core clinical journals. The IOM guideline for systematic reviews recommends assessment of COI in synthesis of evidence. We abstracted COI disclosure exactly as reported by the authors. We did not downgrade quality of evidence according to the COI. Inconsistent reporting of the COI by the same authors within the same time hampered our analysis of the association between COI and trial conclusions.
Reviewer 3	**Adult Appendix Table D155. Comparative safety of amitriptyline vs. botulinum toxin type A for migraine prevention in adults (results from a single high risk of bias randomized controlled clinical trial)**	onabotulintoxinA. your term is out dated	We revised the report clarifying the type of botulinum toxin. Many trials reported using Botulinum toxin type A (BoNT-A; BOTOX, Allergan Inc.) rather than onabotulinumtoxin A. We abstracted intervention information exactly as reported in the original articles.
Reviewer 3	**Appendix C. Analytical Framework Population(s)**	missed sleep disorders, snoring	We could not find good evidence that sleep disorders or snoring may affect the association between migraine preventive drugs and the patient outcomes.
Reviewer 3	**Appendix Table D44. Migraine prevention with Internet-based self management in childhood and adolescence (unclear risk of bias randomized controlled clinical trial). Subheading :Control treatment Control group-Educational intervention**	1.references meaningless without 2. references meaningless, cant track without.	Sine this table presented the results from one trial, the reference was placed in the end of the table name
Reviewer 3	**Children Appendix Table D47. Randomized controlled clinical trials that examined adverse effects of preventive drugs in children with migraine (continued)**	wrong drug wrong population.	We revised this table providing a reference for RCTs by Forsythe (the trial did examine safety of propranolol) and citing two publications of a single RCT (by Apostol et al and the FDA review).

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Appendix Table D50. Strength of evidence about treatment discontinuation due to adverse effects with antiepileptic drugs for migraine prevention in children**	inconsitent reporting versus dose and drug	We clarified in the table that one RCTs demonstrated increased risk of intolerable adverse effects with the highest dose of divalproex.
Reviewer 3	**Children Appendix Table D52. Adverse effects with topiramate versus placebo in children**	inconsistent data reporting utilization across trials	All tables reporting pooled analyses have the same format providing minimum data set for reproducibility of the results in relative scale and absolute scale with weights from random effects models.
Reviewer 3	**Children Appendix Table D53. Strength of evidence that drugs resulted in treatment discontinuation due to lack of efficacy (results from randomized controlled clinical trials)**	cite studies	We added the references
Reviewer 3	**Children Appendix Table D54. Adverse effects with divalproex sodium versus placebo in children (pooled with random effects results from randomized controlled clinical trials)**	did it occur to you that the two studies you report on actually the same study with two authors? don't think so.	We had synthesized the evidence from the FDA review (no authors provided) and two articles by Aposotol and noticed some differences in the reported outcomes. We suspected but had no way to prove that the FDA review and the articles by Aposotol analyzed the same patient data. We revised the report to consider the articles by Aposotol as a publication of the FDA reviewed RCTs. We report the outcomes from both sources demonstrating some differences across the sources.
Reviewer 3	**Children Appendix Table D55. Adverse effects with divalproex sodium versus placebo in children (results from randomized controlled clinical trial)**	how do you get these duplicates based on a single study	The table does not have any duplicates and indicates that all adverse effects with different doses of divalproex are derived from a single RCTs. The FDA review of the same trials did not provide this data.

Commentator & Affiliation	Section	Comment	Response
Reviewer 3	**Children Appendix Table D60. Comparative safety of topiramate versus sodium valproate in preventing children migraine, results from individual randomized controlled clinical trials**	childhood not children	We revised the title as “in preventing migraine in children”
Reviewer 4	**General comments**	Quality of the Report: Good Number of Hours Spent to Review the Report: 6.5	Thank you

Commentator & Affiliation	Section	Comment	Response
Reviewer 4	**General comments**	The report is considerable and I credit the investigators for the time they took to research the subject so extensively. The report provides a significant amount of general information about the performance of classes of drugs, as well as individual drugs. The study also provides an excellent jumping off point for patients who are being newly treated for migraine. Additionally, I appreciate the research documented on page 66. However, I am not certain how clinically meaningful the report will be. The report begins by stating the evidence is weak and there are concerns about industry sponsored studies with no investigator conflicts disclosed. As a patient, I feel research dollars may have been wasted on meta-analysis of studies that could not always be adequately compared. In addition, a physician cannot use this report to determine which course of treatment is best for individual patients because a review of a data set lacking meaningful evidence results in a summary of the same. A large scale, longitudinal study of specific subgroups of migraineurs including quality of life indicators would have better served the patients in my opinion, but the requirements of this grant may have only allowed for literature review. With that said, I feel the investigators performed a thorough study of the available, but lacking, information on migraine treatments.	Thank you. We aimed critically appraise and comprehensively synthesize all available evidence of adults migraine prevention with the FDA approved and off label drugs. We conducted our review according to the well accepted standards. Stakeholders should make decisions based on all evidence rather than one study. Healthcare providers, consumers, researchers, and policy makers deal with unmanageable amounts of information. No everyone has the time, skills and resources to find, appraise and interpret this evidence and to incorporate it into healthcare decisions. A systematic review is a synthesis of all empirical evidence using pre-specified eligibility criteria in order to answer a specific research question. Systematic review uses explicit, systematic methods to minimize bias in order to provide more reliable findings for evidence based policy and decisions. One study, no matter how large or well designed, including longitudinal study of specific subgroups of migraineurs including quality of life indicators can't provide robust evidence for decision making. We pointed out; however, necessity of different study designs including analyses of administrative database in providing evidence for personalized treatment decisions.
Reviewer 4	**Introduction**	The introduction is well written and has excellent reference control.	Thank you

Commentator & Affiliation	Section	Comment	Response
Reviewer 4	**Methods**	The methods are clear and concise. The inclusion and exclusion criteria are justifiable. The strategy is apparent. The statistical methods are appropriate from my limited perspective	Thank you
Reviewer 4	Results	This section contains a high level of detail. The characteristics are clearly described. I very much appreciate the list of excluded studies.	Thank you
Reviewer 4	**Discussion/ Conclusion**	The key messages are clearly stated. The limitations are adequately described. I am not qualified to state whether important literature has been omitted. The future research statement could be expounded upon in my opinion. Migraine is commonly treated by combination therapy and this needs to be further explored.	We added a recommendation to examine comparative effectiveness of combined treatments with approved and off label angiotensin inhibiting drugs vs. monotherapy.
Reviewer 4	**Clarity and Usability**	The report is well structured and well organized. The main points are clearly presented. The conclusions demonstrate a need for further research more than informing practice decisions at this time	Thank you
Public Comment	Conclusions: For episodic migraine, off-label angiotensin inhibiting drugs have the best benefits-to-harms profile	Considering the high degree of evidence published for topiramate relative to off-label angiotensin inhibiting drugs in migraine prophylaxis, the conclusions of the AHRQ report regarding benefit- to-harm of angiotensin inhibiting drugs seems to be overstated and inconsistent with the evidence-based guidance recently published by the AAN & AHS. Silberstein SD, Holland S, Freitag F, et al. Evidence-based guideline update: Pharmacologic treatment for episodic migraine prevention in adults Report of the Quality Standards Subcommittee of the American Academy of Neurology and the American Headache Society. *Neurology* 2012;78:1337-45.	We revised the report clarifying that exploratory network meta-analysis found low strength of indirect evidence that off label angiotensin inhibiting drugs and beta-blockers are relatively effective and relatively safe for migraine prevention in adults. We emphasized that future research are needed to confirm better benefits and safety profile with specific drugs from these drug classes.

Commentator & Affiliation	Section	Comment	Response
Public Comment	Conclusions: Approved and off-label beta blockers are effective without bothersome harms.	Among other adverse events, beta blockers may be associated with depression, possible exacerbation of asthma, COPD, and heart failure. Based on these known adverse events the conclusion that beta blockers are without bothersome harms seems to minimize potential safety risks.	We clarified that all trials included patients without contraindications to the examined drugs. We clarified that our review has implications for clinical practice. Informed decisions in clinical settings should take into account the rates of benefits and harms attributable to specific drugs. The most recent guideline recommends approved by the FDA antiepileptic topiramate and divalproex and beta-blockers propranolol and timolol for adult migraine prevention. Our review provided evidence for using effective and relatively safe off label angiotensin inhibiting drugs and beta-blockers as alternative options based on patient preferences, comorbidities, and contraindications to the medications.
	Conclusions: Approved antiepileptic drugs are	The conclusion makes a general characterization of AEDs that may be overstated and not properly represent the data. Data from a pooled safety analysis of topiramate showed that out of 1,135 patients who received topiramate, 25% discontinued due to one or more adverse events, compared with 10% of the 445 placebo-treated patients. Placebo patients were more likely than topiramate patients to withdraw due to other reasons including lack of efficacy. Overall, topiramate is generally safe and reasonably well tolerated for the prevention of migraine in adults. Most topiramate-associated adverse events were mild or moderate in severity, and they occurred more frequently during the titration period than during the maintenance period. Adelman J, Freitag FG, Lainez M, et al. Analysis of safety and tolerability data obtained from over 1,500 patients receiving topiramate for migraine prevention in controlled trials. Pain Med. 2008 Mar;9(2):175-85	We concluded safety of the drugs based on all available evidence. We analyzed specific safety outcome (specific adverse effects or treatment discontinuation due to adverse effects) rather than “general safety” or “reasonable tolerability” of the drugs.

Commentator & Affiliation	Section	Comment	Response
	Part B – Children Off Label Pharmacological Agents Antiepileptic Drugs – Topiramate Topiramate, 100 to 200 mg/day, was no more effective than placebo in reducing monthly migraine attacks by ≥50 percent (two RCTs of 298 children, moderate strength of evidence).	We suggest separating the comments from the two studies to provide a more accurate reporting of the data. The pilot study by Winner et al (2005) did not show a statistically significant difference in the 50% responder rates, however, the results were quite different in 2009 study by Lewis, et al. Lewis, et al demonstrated a statistically significantly higher 50% responder rate for the 100 mg/day topiramate treatment group, compared with the placebo treatment group (p=0.002), but not for the 50 mg/day topiramate treatment group (p= 0.957). Comparisons based on any definition of *responder* showed that the 100 mg/day topiramate treatment group had consistently higher response rates than did the placebo and 50 mg/day topiramate treatment groups. Lewis D, Winner P, Saper J, et al. Randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of topiramate for migraine prevention in pediatric subjects 12 to 17 years of age. Pediatrics. 2009 Mar;123(3):924-34.	The study by Winer from the Topiramate Pediatric Migraine Study Investigators had a larger sample size than the study by Lewis. Pooled estimate was homogeneous (non statistical tests for heterogeneity). We clarified that "Topiramate, 100mg/day increased the likelihood of ≥50 percent reduction in migraine attacks on one RCTs from 2 that examined this association."
Reviewer 5	Part A: Executive Summary Introduction	This report could use more background information on the topic -- what are risk factors for migraines? How is it diagnosed? Maybe some information about what each of the drug classes or individual drugs are and their mechanism of action on how they help migraines.	That material is not immediately germane to the topic.

Commentator & Affiliation	Section	Comment	Response
Reviewer 5	Methods	How were your expert panels identified? How did they provide input? Who was on the panel (doctors only?)? Who are key informants?	We clarified that the topic was anonymously nominated via the public domain. We invited researchers, practitioners, payers, and patient advocate groups to serve as key informants. We discussed research questions with key informants, posted research questions on line in the AHRQ website, and finalized according to the public comments. After discussion with key informants we formulated a list of eligible pharmacological classes. We conducted a comprehensive literature review following the principles in the Methods Guide for Effectiveness and Comparative Effectiveness Reviews (hereafter Methods Guide) developed by the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center Program and PRISMA guidelines (CRD42012001918).
Reviewer 5	Part A: Results	More study details would be helpful, it was difficult to have to navigate through so many tables and appendices to figure out who was in the study, the dosing/timing of the drugs, etc.	We revised the report providing summary tables with the references for easy navigation.
Reviewer 5	Part A: Results	The key notes were nice but are there any other issues with the evidence that should be considered? Would a patient take it personally if I prescribe a random drug for their migraine (e.g., antiepileptic when they don't have epilepsy; or dementia drugs in healthy non-demented adults?)?	We clarified that our review has implications for clinical practice. Informed decisions in clinical settings should take into account the rates of benefits and harms attributable to specific drugs. The most recent guideline recommends approved by the FDA antiepileptic topiramate and divalproex and beta-blockers propranolol and timolol for adult migraine prevention. Our review provided evidence for using effective and relatively safe off-label angiotensin inhibiting drugs and beta-blockers as alternative options based on patient preferences and comorbidities.
Reviewer 5	Part A: Tables	The table footnotes indicated there were items in bold that were significant -- my computer screen wouldn't show the bolding.	We sincerely apologize. We added an explanation of statistically significant differences when 95% CI of attributable events per 1000 treated do not include 0.
Reviewer 5	Part A: Figures	Could you list you questions again in Figure 1.	We added all research questions to Figure 1.
adf adg	Part A: Executive Summary	Nice overview of the information.	Thank you