Washington State Health Care Authority

Treatment of chronic migraine and chronic tension-type headache

Draft evidence report: Peer review, comment and response

April 14, 2017

Health Technology Assessment Program (HTA)
Washington State Health Care Authority
PO Box 42712
Olympia, WA 98504-2712
(360) 725-5126
www.hca.wa.gov/about-hca/health-technology-assessment
shtap@hca.wa.gov

Treatment of Chronic Migraine and Chronic Tension-Type Headache

Provided by:

Spectrum Research, Inc.

Prepared by:

Andrea C. Skelly, PhD, MPH
Dena Fischer, DDS, MSD, MS
Erika Brodt, BS
Cassandra Winter, BS
Aaron Ferguson, BS

April 14, 2017

With assistance from:

Krystle Pagarigan, BS
Mark Junge, BS

Responses to clinical and peer reviewers

Spectrum Research is an independent vendor, contracted to produce evidence assessment reports for the Washington Health Technology Assessment (HTA) program. For transparency, all comments received during public comment periods are included in this document and attachments. Comments related to program decisions, process or other matters not pertaining to the evidence report, are acknowledged through inclusion only.

Specific responses pertaining to peer reviewer comments are included in Table 1.

Responses to public comment may be found in Table 2.

Full text of peer review and public comments follows the tables.

Draft report peer reviewers:

- Janna Friedly, MD; Assistant Professor, Department of Rehabilitation Medicine; Physiatry, Physical Medicine and Rehabilitation; University of Washington
- Robert Nicholson, PhD, Mercy Hospital, Director of Clinical and Applied Insight, Department of Patient Quality and Safety, Chesterfield, MO; Clinical psychologist, Certified Clinical Trials Investigator

Table 1. Responses to Clinical and Peer Reviewers

	Comment	Response
Janna Friedly, MD		
	Specific comments	
General comments	The table of contents numbering was a little bit confusing – the executive summary in the report included pages 1-1 through 1-56, but the TOC states 1-9. There are no line numbers so detailing the comments was a bit challenging.	This has been addressed.
Executive summary, general comments	In general, the executive summary findings are difficult to read and interpret. This is in part because many of the outcome measures and definitions have not yet been described or are buried in the text– so as a stand alone document, it is hard to interpret the findings. For example, the definitions of short, intermediate and long term outcomes were provided on page 1-13, but the key findings do not use the terms short, intermediate and long term, so it requires remembering the definitions to be able to classify the findings. In general, I think it is easier for people to interpret the findings in terms of short, intermediate and long-term findings (as this is how we think clinically) rather than by number of weeks.	Thank you for your comments. We have added some context to facilitate interpretation and added terminology for short, intermediate and long-term based on the definitions for this report.
Executive summary, page 1-11	• Studies reporting populations with a mean of ≥12 headache days per month or ≥12 headache episodes or attacks per month were considered to meet the criteria for chronic headache. Why this definition? Is there a citation for this?	Thank you for your questions. The nomenclature and classification of headache has evolved over the past two decades. Headache attacks may last for one or more days and/or patients may report the number of days for a specific headache type in addition to the number of overall headache days. Some authors used 30days as a month, others used a 28 day period. We considered any combination of specific headache days and general headache days (means and standard deviations). For example, patients may report 11/28 days with migraine, but a total number of headache days of 21 days/28 day period. Authors

	Comment	Response
		may also have reported based on a 30-day period. Inclusion criteria for the majority trials specifically stated inclusion of patients with ≥15 headache days and/or specified the IHS classification in effect at the time of the study. Those that did not reported mean of at least 15 headache days and/or specific headache days or provided other information that was used to judge whether the headache as chronic (e.g. headache days occurred at least 50% of the days per month.) Across included studies, the criteria for chronic headache related to at least 15 days per month was met.
Executive summary, page 1-14	• At 24 weeks, across 2 RCTs, there is moderate evidence that more BoNTA recipients achieved ≥ 50 % reduction in number of migraine days and overall number of headache days compared with placebo, however there was not a difference between groups in the percent of patients who achieved ≥ 50 % reduction in the number of migraine episodes across 3 RCTs (moderate evidence). • Through 24 weeks, there were no statistical differences in the reduction of mean number of headache episodes (3 trials) or migraine episodes (2 trials) per month; however a small difference between groups for reduction (<2 days) in the mean number of headache days and migraine days per month favoring BoNTA was observed (moderate evidence for all outcomes). These two bulleted findings are difficult to interpret. It is hard to understand the difference between the first and second – it takes quite a bit of reading to understand what these findings mean. I think these findings could be reworded to have parallel structure and highlight that there was a difference in terms of	Thank you for your comments We have edited bullets for clarity regarding outcomes. Some additional context regarding outcomes reported has been added. Scales for measures used in the strength of evidence tables have been added as footnotes to the tables. Table 1 in the full report provides a reference for outcomes measures.

	Comment	Response
	migraine and headache days (with either definition), but not in terms of migraine or headache episodes (with either definition). Summary of results: this comes before much of the info on outcomes so Headache Impact Test-6 Scores has not yet been defined. This makes it a little bit difficult to put these findings into context.	
Executive summary, page 1-16	This statement is under the SMT vs amitriptyline category. "At 4 weeks, acupuncture resulted in a statistically greater proportion of patients achieving >20% and >40%, but not >60%, reduction in Headache Index scores from baseline compared with amitriptyline."	This has been corrected to read that SMT resulted in greater proportion of patients
Executive summary, page 1-16	**Chronic Tension-type Headache** ***BoNTA versus Placebo*** • Short-term (8 weeks), although more patients the BoNTA experienced ≥ 25% reduction in pain intensity, results did not reach statistical significance in 1 small RCT (insufficient evidence). • At 12 weeks, although more patients the BoNTA experienced ≥ 45% reduction in pain intensity, results did not reach statistical significance in 1 small RCT (insufficient evidence) • At 12 weeks, across 2 RCTs, BoNTA was associated with a reduction in the mean number of headache days per month (insufficient evidence). It is unclear why the first 2 bullet points only refer to one study and the 3rd refers to 2 RCTs. This is a more general point, as this occurs in other sections – it is hard for the reader to understand with these summaries what the n is and why some findings only draw from a subset of the RCTs. There is a description in the report itself about how different studies used different outcomes and that is why there are different descriptions of % improvement and number of RCTs reporting certain outcomes, but this is not provided in the executive summary.	We have added context to the executive summary to clarify that not all studies reported all outcomes at each time frame. The number of studies listed reflects the number of studies for which that specific outcome was reported at that time frame. Not all trials report the same outcomes so the n (patients or number of studies) may vary across outcomes and time frames.
Introduction, general comments (appraisal	A minor comment is that the paragraph that described OnabotulinumtoxinA (onaBoNT-A, Botox) on page 1 includes the statement "It has been associated with reduction in the number chronic migraine headaches	Thank you for your comment. We have edited this.

	Comment	Response
section: pages 1-9)	attacks" which I think is best left out in the introduction as this is an assessment of the literature that will be reviewed in this study.	
Background, general comments	In general, this is a well written background that addresses the need for this review and the importance of assessing commonly used treatments for migraine and chronic headaches. The definitions of the different types of headaches and the classification of chronicity was well described. There are clear descriptions of each of the different interventions considered in this review and the rationale for why these were included.	Thank you for your comments
Background, page 37	With the above in mind, the primary results for use of BoNTA for the prevention of chronic migraine from the 2013 AHRQ report are summarized in Table X. Minor comment: Table X	Thank you for your comment. We have provided the table number.
Report Objectives & Key Questions, general comments	The key questions are clear and relevant	Thank you for your comment
Methods, general comments	The methods are clearly described and are appropriate to answer the key questions. One challenge is the diversity of outcome measures being assessed and the range of outcomes reported in the studies which makes comparisons difficult. This is not a flaw of the report or methodology necessarily, but reflects the challenges with the evidence and ability to compare studies. It is clear that there are few measures that have clear MCIDs and so the ability to interpret the outcomes and the magnitude of the treatment effects is problematic.	Thanks you for your comments. Yes, these are indeed challenges.
Results, general comments	The key questions are answered to the extent that they can be with the existing literature. In general, the summaries of the result are difficult to interpret because the statements are not referenced and the number of trials included (particularly for Botox vs placebo for migraines) in each summary statement (between 1-3) doesn't match the total number of trials included in the review (n=4). In addition, when there are "positive" findings, it is difficult to interpret the magnitude of the effect or the clinical implications of these findings. I found that the	Not all studies reported all outcomes at each time frame. The number of studies listed reflects the number of studies for which that specific outcome was reported at that time frame. Not all trials report the same outcomes so the n (patients or number of studies) may vary across outcomes and time frames.

	Comment	Response
	summary tables that are included in the executive summary starting on page 1-26 present the conclusions in the most clearly understandable language and summarizes the magnitude of the findings and clinical significance. If the results section and the bulleted summary statements could use similar language, I think this report would be easier to interpret. As I have pointed out below, there are many inconsistencies in the data presented and I found the tables and graphs a bit hard to interpret. I would recommend being as consistent as possible with formatting and adding footnotes when you have to stray from the common formatting in order to orient the reader.	We have attempted to edit the report and figures for clarity and consistency and provide context on magnitude of effect. The purpose of the bulleted points is to provide an overview of findings in lieu of repeating data that are in the tables.
Results, page 71	It would be helpful to describe the magnitude of the treatment effect to put the MIDAS and HIT-6 results in perspective in terms of clinical importance.	Thank you for your comments; Effect sizes and, when available, information on clinically important differences, are provided in the report text and strength of evidence tables that follow the bulleted information. The bullets are intended to provide an overview. Table 1 of the full report serves as a reference for reported outcomes measures.
Results, page 72	This applies to this page but also to others that have the summaries of key findings – be consistent with use of periods at end of the summary statements. This is inconsistent throughout the document. Another style suggestion for the bullets below – would suggest not bulleting the 1st as this is a heading for the 2nd two bullet points or more clearly designating this as a heading. • BoNTA versus Amitriptyline (1 RCT): • At 12 weeks, there were no differences between groups with regard to the percent of patients with ≥50% reduction in the frequency of pain days or the percent of patients with ≥3 point reduction in pain intensity; (low evidence for both outcomes)	Thank you for your comments.

	Comment	Response
	• No data on short- or intermediate term outcomes were available	
Results, page 72	• At 12, 24, and 36 weeks, there was low evidence that more BoNTA recipients achieved ≥50% reduction overall number of headache days compared with placebo, however the differences did not reach statistical significance perhaps in part due to sample size. • There were no differences at any time points up for the functional measures reported including MIDAS, HIT-6 and MIQ (low level evidence for all outcomes) Presumably, since there was just one RCT in this category, these two statements above refer to the same RCT. Was the lack of difference in functional measures due to small sample size as well or did the lack of differences and confidence intervals suggest this is a definitive finding?	Thank you for your question. The study was small (N = 60 randomized); there was substantial lost to follow-up and differential loss to follow up with data avialale for the BoNTA and topiramate groups respectively of 80% vs. 70% at 12 weeks, 70% vs. 60% at 24 weeks and 63% vs. 57% at 36 weeks. The findings are not likely to be definitive. (Context of this nature has been highlighted in the report.)
Results, page 73	**Transcranial Magnetic Stimulation versus Sham** • At 4 weeks in one RCT, transcranial magnetic stimulation (TMS) resulted in a statistically greater improvement in all outcomes measured compared with sham (low quality evidence for all): proportion of patients achieving a >50% reduction in migraine attacks and in headache severity; reduction in the mean number of migraine attacks per month; and the proportion of patients improving to a functional disability rating of normal or mild. • At 8 weeks in a second RCT, no statistical differences were seen between low-frequency TMS and sham for reduction in migraine attacks per 2 weeks and reduction in migraine days per 8 weeks; however, all data is of insufficient quality to draw conclusions. This second bullet point is difficult to understand. "attacks per 2 weeks" and "days per 8 weeks" isn't clear. It is also difficult to reconcile the findings of the 1st RCT versus the findings of the 2nd RCT.	Thank you for your comments. We reported the results as they were reported in the studies; The author's presentation of data did not permit describing the results using a common metric or format. We agree that this presents a challenge.
Results, pages 73-75	The descriptions of the studies in this section could be more clearly written to help the reader understand the difference between PREEMPT 1 and PREEMPT 2. Table 9 includes data from PREEMPT 1, PREEMPT 1 and 2 and	Thank you for your comments. We have made edits to clarify and correct the report.

	Comment	Response
	PREEMPT 2. It isn't clear why you have chosen to include the combined data or what that adds. It is also unclear if the Aurora 2014 reference in this table is ALSO PREEMPT 1 and 2 as the n's are the same and the data very similar, but slightly different. It is also not clear why the Frietag 2007 study reports only combined data in one column rather than by assigned group as the other studies did. If this is because the data was not reported this way, a footnote should be included to explain this. Also – is the Freitag 2007 study (n=60) different than the Freitag 2008 study (n=41)? I was unable to find the references for each of these studies. Aurora 2014 – is this n=1384 a typo? In the following graphs, the n=1005. These types of errors make this report very difficult to follow. It took reading this several times and then pulling the original papers to understand these studies and the data reported.	We have added text to clarify the PREEMPT studies, a table outlining each publication and use of the various reports. Briefly, we used the primary studies for analysis where possible to demonstrate results of the 2 studies independently so that readers can see similarities and differences in results across these 2 trials; Published data pooled across PREEMPT 1 and 2 were only used for outcomes for which primary data were not available. Freitag: • Correct citation is Freitag 2008; the 2007 was a typographic error and has been corrected. • They randomized 60 patients, but only 41 received treatment; 19 were excluded after randomization due to medication overuse. We have noted this in relevant tables/text. • Regarding table 9 (and others) summarizing patient and study characteristics; data were not provided by treatment arm for some characteristics, thus data across treatment arms is presented. Aurora 2014: The n's reported reflect the number of patients for the open label phase of the study who has completed all injection cycles during the randomized phase and the open label phase; it is essentially a sub-analysis and case

	Comment	Response
		series from the perspective of this report. We've added a table clarifying different components of the PREEMPT trial
Results, page 76	This statement below is unclear as written. I would suggest restating to say that although the proportion of patients who experienced >50% reduction was higher in each of these studies, these findings were not statistically significant or did not reach statistical significance… The proportion of participants who experienced ≥50% reduction in number migraine episodes from baseline was higher following BoNTA compared to placebo, but groups were statistically similar across three trials.24,63,73	Thank you for your comments. We have reworded this.
Results, page 76	Results did not reach statistical significance in one small moderately low risk of bias trial at 16 weeks (RR 2.0, 95% CI 0.6, 6.8).73 In figure 5, the Freitag 2008 study which the above sentence references is classified as "moderately high risk of bias" versus the statement above which calls it "moderately low risk of bias"	Thank you for your comments. We have corrected the risk of bias; it was considered to be at moderately high risk of bias
Results, page 81	Presenting figures 7 and 10 in opposite directions is a bit confusing. (i.e. one on the positive y axis and the other on the negative y axis). I would be consistent to make these graphs easier to interpret.	The data in figure 7 represents proportions of patients achieving a specific threshold for treatment response; Figure 10 represents the change in a continuous variable (means). We have put the data in tables in lieu of figures.
Conclusions, general comments	I did not see any section in the report that corresponded to "conclusions." If this is referring to the summaries of the key findings, I have commented on these in the above sections. I do think it would be really helpful to have a conclusions section that summarizes the breadth of the available data, the overall quality of the data and the magnitude of findings in order to put this in context. This is a comment that pertains to all of these large reviews and is not specific to this particular review, but somehow it needs to be more clearly presented which of the findings are limited by high risk of bias studies. Although each of the studies is graded in terms of risk of bias and the strength of the evidence is graded in terms of insufficient, low, moderate, etc it takes quite a bit of	Thank you for your comments. We have added some general context to the Executive summary and results section regarding study quality and findings for which there is moderate evidence. Conclusions refer to the summaries of key findings in the strength of evidence tables. We have noted the risk of bias for studies in theses tables. The

	Comment	Response
	reading and re-reading to really understand the big picture of this report. In general, there is insufficient or low quality evidence for all key findings with the exception of those related to the PREEMPT trials for botox. This somehow should be conveyed a bit more transparently	strength of evidence may vary for different outcomes based on the other GRADE domains (e.g. precision) even though the individual study risk of bias may be the same. The full GRADE tables in section 5 provide transparency for the final strength of evidence.
	Quality of the Report Superior **0** Good **1 (once the errors are corrected!)** Fair **0** Poor **0**	
Robert A. Nicholson, PhD		
	Specific comments	
Introduction, page 1	• "Tension-type headache….accounts for 90% of all headaches." Would recommend a citation for this reference. Also, given that this report is on treating patients who present for headache care, it may be useful to note that although Tension-Type Headache (TTH) is more common than migraine, most individuals who present for care do so for migraine. Most TTH headaches are adequately controlled with OTCs and rarely present for care. Moreover, given that the report is focused on chronic headache, this statement may deter the audience's focus on the population being considered. **Psychological Treatment** • "Migraine management generally focuses on pharmacological therapy". There are a host of articles, reviews, and expert opinions regarding the value of psychological therapy for migraine. A summary can be found here http://www.headachejournal.org/view/0/EvidenceBasedBehavior.html. • The sentence a line above states "Usual management of TTH includes pharmacotherapy, psychological therapy…". This could easily be changed to ""Usual management of TTH and migraine includes pharmacotherapy, psychological therapy…" and be accurate.	Thank you for your comments. We have edited the background accordingly and added additional context.

	Comment	Response
Introduction, page 2	**Policy Context** • Interventions being assessed. Reading through the evidence report, it became clear what was being studied. However, the context for inclusion was not fully clear. It seems that the focus could be stated as "interventions in which the heath care professional is physically intervening in some manner". The focus is not non-pharmacological interventions as Botox and trigger point injections both include pharmacologic agents. Moreover, this does not included psychological interventions and so there really is a specific realm in which this evidence reports is focused. However, it is difficult to find a strong logic case for the value in choosing this particular set of interventions. • Similarly, although it becomes clear as one reads the report that the primary focus is on reducing headache episodes/frequency, it would be helpful to state this in the background/rationale section prior to the objectives.	Thank you for your comments. The interventions to be included were specified by the Agency. Regarding the focus on reducing headache frequency: This was the most commonly reported outcome reported across studies.
Introduction, page 5	**Outcomes Assessed…**. • Point 2 states "Complete cessation//prevention of headache: This operationally included reduction in mean number…." This seems incongruent. If there is complete reduction then the reduction in mean number would be 100%. Reading through the report it does not appear that complete cessation/prevention is measured. • Of note, any intervention that has aimed for complete cessation/prevention has always failed. There are a host of potential reasons as to why this is a nearly impossible aim and not one worth evaluating relative to other outcomes. **Table 1.** • Outcomes measures. Ultimately, the primary outcome for these studies was reduction in headache episode or day frequency. The outcome measures noted in Table 1 were measures in addition to the primary outcome, which seemed odd upon first review.	Thank you for your comments. Complete cessation of headache was listed *a priori* as a key outcome; unfortunately, none of the studies reported on this outcome. Reduction in the mean number of headaches or episodes was reported. We have edited the text to better reflect this. Table 1. Is an alphabetical listing of validated measures used in included studies and includes a variety of measures; it is intended as a general reference. We have added additional context prior to the table for clarification.

	Comment	Response
	• Outcome measure domains. This reviewer was surprised to see functional, disability, quality of life, pain-related, and psychologically related outcomes all being combined into one table. Each of these is inherently measuring something different and one could easily expect the outcomes to vary and not be related specifically to whether the intervention was effective at reducing headache. Perhaps separating those or at least acknowledging that they are measuring different constructs and the limitations inherent in considering them together would be useful.	
Background, general comments	The overall background is well written and clear. The discussion regarding the evolving nomenclature and vernacular surrounding the classifications and labels of various chronic headache types is valuable to set the context for the review.	Thank you for your comments.
Background, page 18	Near the bottom of the page it is stated "Several newer interventions have recently surfaced." Among those listed are acupuncture, massage, manipulation, trigger point injections. Although one might argue that the systematic evaluation of these for preventing chronic headache is relatively new, these interventions have been used clinically for a long period of time.	Thank you for your comments. We have edited this, removing reference to these as newer interventions.
Background, pages 21 & 23	**Medication Overuse** • Medication overuse can influence progression from episodic to chronic headaches. This is seen consistently in clinical practice and its relevance has emerged over the past decade. In the review, this is noted as being potentially relevant for barbiturates and opioids. However, it would be useful for the review to note that few trials appeared to specifically ask about potential medication overuse and as such, a potential treatment confounder was not typically accounted. At the same time, this lack of accounting for medication overuse headache must take into context the evolving nature of the field's understanding of this phenomena a decade ago. • Although the authors note that NSAIDs and triptans do not appear to be related to medication overuse headache, here is a citation that suggests the	Thank you for your comments. We have provided additional information on risk for CM development related to NSAID and triptan use. We have provided additional context throughout the report related to the issues raised regarding medication overuse. We have noted which studies excluded patients with medication overuse and attempted to provide information on it as reported in the studies. Studies varied with respect to definitions of medication overuse as well as

	Comment	Response
	evidence may be mixed https://www.ncbi.nlm.nih.gov/pubmed/23992516 • The authors may want to specifically note that although the role of medication overuse in contributing to chronic headache progression and maintenance is of varying importance, it is something that would be ideally accounted for when selecting patients for trials such as those under consideration for the current review. The authors may want to note that unscreened and/or untracked medication overuse could have a non-zero impact on trial results. However, the authors would do well to acknowledge that for some of these studies, particular those initiated and conducted in the early 2000's, the potential influence of medication overuse was not appreciated to the degree it is now.	inclusion of patients with medication overuse.
Background, page 23	**Psychological Treatment for Chronic Headache** • Please see the comments noted in the background/rationale section earlier about how these treatments (including biofeedback) are potentially useful for CM and CTTH. **Headache Type Classification** • The review notes that those presenting with both migraine and tension-type headache are considered chronic daily headache and is not an ICHD 3 classification. This is accurate. However, one wonders about whether this is a function of some older studies that were conducted prior to the newest ICHD classification and/or prior to a consistent nomenclature being discussed in the literature (which emerged over the 2000's). This is relevant in that those who are classified as CM or CTTH often experience both types of headaches (or at least headaches that don't always fit every time into the diagnosed category). It is the predominant type that ends up getting diagnosed and thus classified. • Given the journey to achieve a consensus nomenclature and subsequent ICHD 3 classification was occurring in parallel with the time frame for many of these studies, it might be useful to more clearly state the dates for which the various names	Thank you for your comments. We have made edits and added additional context.

	Comment	Response
	and classifications emerged relative to the studies evaluated. Perhaps a study from the early 2000's may have been considering a "CDH" group that now might be "CM".	
Background, page 33	AAN…The "N" here refers to Neurology rather than Neurosurgeons https://www.aan.com/Guidelines/Home/ByTopic?topicId=16	Thank you. We have corrected this.
Evidence, general comments	• Aims/objectives all seem to address relevant policy and clinical issues. • Please see previous comments related to content on page 5 regarding outcomes assessed. • See same section comments for page 5 regarding outcome domains assessed. The table on p. 63 does a better job of delineating the domains.	Thank you for your comments. We have made some edits for clarification.
Evidence, page 66	• It was unclear how total citations with n = 47 led to exclusions of n = 2795. One suspects that n = 47 was in actuality n = 2947, of which 2795 were excluded, but this would benefit from being made more clear. • Appendix E. Although it is expected that the rationale for not including Appendix E was space, the tables in Appendix would have been highly useful to include in the report and/or use the structure of that table to improve the utility of tables included in the results section.	Thank you for your comments Regarding the number of citations – this has been corrected.
Methods, general comments	• Method for identifying relevant studies is adequate? Yes • Criteria for the inclusion and exclusion of studies is appropriate? Yes • Method for Level of Evidence (LoE) rating is appropriate and clearly explained? For the most part. Including the information in Appendix E within the report would help improve clarity. • Data abstraction and analysis/review are adequate? Yes	Thanks you for your comments.

	Comment	Response
Results, general comments	• Amount of detail presented in the results section appropriate? For the most part. The sections aren't as uniformed in their look and feel as one might expect. Not every section feels like it was handled in the same manner. In situations like this where there are lots of repetitive sections, one would expect there to be easily observed consistency in the format. • Key questions are answered? Yes, very well. • Figures, tables and appendices clear and easy to read? No. Tables 9, 11, and others like it are confusing for the reader. The tables in the appendix are much easier to follow. Would recommend putting the reference number next to the study author names in the tables. • Have gaps in the literature been dealt with adequately? The authors appear to have dealt with the known literature and noted where there are deficiencies in the literature. • Recommendations address limitations of literature? Not applicable at this time. • Explanation of RoB. For some of the trials the RoB was explained (eg, p. 90 and others); however, there were examples where this was not the case (eg, p 86). Would recommend they all be explained and consistently presented.	Thank you for your comments. We have made numerous edits to enhance the consistency of sections. Tables 9, 11 and similar are intended to provide a side-by-side summary comparison of primary patient characteristics and study features to provide context for study results. We have edited them to enhance clarity. For some readers the Appendix tables provide additional information and clarity We have edited the results to include a more detailed description of risk of bias concerns and have added context regarding overall study quality across included studies
Results, page 102	This is the one place where this reviewer found a note that the presence of medication overuse had an unknown impact on outcomes.	We have provided additional context regarding medication overuse as reported in the included studies.
Results, page 169	Under results: Base Case, $ was used instead of £.	Thank you. This has been corrected.

	Comment	Response
Results, page 215	This section seemed oddly placed, inserted after the evidence tables.	Thank you for your comment. There is no established GRADE method or table format for reporting strength of evidence across economic studies, thus we present the summary of economic studies in a text format.
Conclusions	• Are the conclusions reached valid? Not applicable at this time	
Presentation & Relevancy	• Is the review well-structured and organized? For the most part, yes. See comments regarding Tables 9, 11, and others like it regarding confusion. • Are the main points clearly presented? Yes • Is it relevant to clinical medicine? Yes • Is it important for public policy or public health? Yes	Thank you for your comments.
	Quality Of the Report Superior Good **X** Fair Poor	

Responses to public comment on draft report

This second section responds to comments received from the public comment period by the following:

- Amgen, Suzana Griffin, PharmD, Executive Director, Global Scientific Communications, Thousand Oaks, California

Complete comments and related cover letter as submitted are attached following the responses below. *For transparency, all comments received during public comment period are included in this document and attachments. Comments related to cost data presented in the report by the Technology Assessment Program, program decisions, process or other matters not pertaining to the evidence report, are acknowledged through inclusion only.*

Table 2. Responses to public comments

	Comment	Response
Amgen, Inc.		
	Specific comments	
	We recognize that the HTA remit encompasses medical devices, procedures and tests, not pharmacological products, and that the draft report accordingly focuses on the treatment of chronic migraine and chronic tension-type headache with OnabotulinumtoxinA, trigger point injections, transcranial magnetic stimulation, manual therapies and acupuncture. Despite not having a pharmacological intervention included in the assessment, we would like to comment on the draft report for the following reasons: The treatment of migraine is multimodal and multidisciplinary. Clinicians consider a range of treatment options and frequently switch patients between alternative treatment options. • Amgen is committed to having an ongoing dialogue with patients, providers, payers, policymakers and regulators to find ways to stimulate innovation of all types, while also alleviating the financial and societal burden of some of the world's most serious diseases. We therefore seek to engage constructively on the overall approach of HTA initiatives. • The draft report explains, "Migraine management generally focuses on pharmacological therapy. In chronic headache disorders, including chronic	Thank you for your comments.

	Comment	Response
	tension-type headache (CTTH) and chronic migraine (CM), the focus of treatment is on preventative measures." Amgen recognizes that this is an area of high unmet need for people with migraine.	
Overall Approach	Given the stakes for patients, Amgen believes that all economic reviews on the value of medicines should aim to achieve the highest level of transparency, strive for very broad stakeholder engagement, and place scientific rigor and patient interests at the center of the analyses. We believe that a thorough and balanced technology assessment should rely on direct data from rigorous comparative trials when available, calibrated and adjusted for real world application in the heterogeneous markets and treatment settings where the technologies are expected to be used. Amgen applauds the HTA program for its systematic review of the literature based on transparent inclusion/exclusion criteria and its reporting, with rigorous evaluation of each included study's results. • For example, the review of chronic migraine cost-effectiveness studies provides the weaknesses of each study evaluated in the HTA and notes when the source is from a study with pooled data. A thorough and balanced technology assessment should rely on direct data from rigorous comparative trials when available, calibrated and adjusted for real world application in the heterogeneous markets and treatment settings where the technologies are expected to be used.	Thank you for your comments.
	The draft report failed to note certain instances where validated study data were not included (see the bulleted list under Cost of Disease section for details). • A more thorough HTA needs to evaluate all strengths and weaknesses of the economic studies included in the assessment. • It is imperative for a robust HTA to integrate real-world observational evidence in addition to results from randomized control trials in order to capture and model the broad impact of a disease on patients and society in the setting of actual practice.	Thank you for your comments. The report summarizes and critically appraises full economic studies meeting the inclusion criteria set *a priori*. The QHES, (which includes a question regarding use of study data) was used to facilitate appraisal of included studies and limitations of them are described in the report. Two studies were of poor to moderate quality and one was of very poor quality. Methods for

	Comment	Response
		appraisal are outlined in the Appendices. We have added comments to the appraisal related to inadequate characterization of indirect cost where appropriate. De novo economic analysis was within the scope of Spectrum's work for this project and not therefore not performed.
Cost of Disease	Often HTAs only view the cost of disease from a narrow silo or focus on the short-term financial or budget impact of paying for interventions by estimating direct-cost offsets – i.e. the net financial result of replacing one intervention with another. It is imperative for the scientific rigor of any HTA to evaluate the overall burden and cost of disease holistically and not just the cost of the interventions to create a sustainable health care system. In addition, it is essential to consider the inefficiencies associated with migraine-care delivery and how some of these inefficiencies may be rectified by the use of a more innovative therapy. This HTA does acknowledge the broad societal impact of headache disorders. The HTA also cites several studies estimating indirect costs of migraines, primarily due to reduced work productivity (presenteeism) and missed workdays (absenteeism).	Thank you for your comments. This was not within the scope of work for this report.
	The HTA also cites several studies estimating indirect costs of migraines, primarily due to reduced work productivity (presenteeism) and missed workdays (absenteeism). However, the systematic review has identified only clinical and cost-effectiveness studies and fails to include recent studies that have further validated the significant indirect costs associated with episodic migraine and CM. • Migraine patients incur significantly higher indirect costs (absenteeism, short-term disability, and long-term disability costs) than matched non-migraine patients ($11,294 vs $8,945) • Migraine patients are more likely to have short- and long-term disability claims, and incur ~$1,300	Thank you for your comments. We included all full economic studies identified via our broad literature search that met our inclusion criteria. They studies cited did not meet our inclusion criteria.

	Comment	Response
	higher per patient disability-related costs than non-migraine patients. • The indirect economic burden (absenteeism and presenteeism) of migraine is estimated to be ~$13Bn in the US, costing employers up to $4K and $13K per year for episodic and chronic migraine sufferers, respectively. **Citations:** Bonafede, MM et al. Incremental Direct and Indirect Costs Associated With Migraine in the United States. Presented at: ISPOR 19th Annual European Congress, October 2016, Vienna, Austria Serrano D, et al. Cost and predictors of lost productive time in chronic migraine and episodic migraine: resultsfrom the American Migraine Prevalence and Prevention (AMPP) Study. Value Health. 2013;16(1):31-8.	
	In addition, a 2017 systematic review of 28 studies found that presenteeism costs are rarely included in full economic evaluations, although the impact of presenteeism in the workplace and society is high. With respect to migraine, Kigozi et al observed: "Presenteeism, from this review, appears to contribute significantly to productivity costs (or savings) and overall total costs of certain disease areas such as musculoskeletal pain, migraine, and mental health–related disorders. Economic evaluation recommendations in these disease conditions that do not include estimates of presenteeism may result in less than optimal resource allocation decisions from a societal perspective." **Citation:** Kigozi J, et al. The Estimation and Incl Kigozi J, et al. The Estimation and Inclusion of Presenteeism Costs in Applied Economic Evaluation: A Systematic Review. Value Health. 2017;20(3):496-506.usion of Presenteeism Costs in Applied Economic Evaluation: A Systematic Review. Value Health. 2017;20(3):496-506.	Thank you for your comments. The study cited did not meet our inclusion criteria.
	The HTA could demonstrate the public employee impact of migraine on indirect costs in the State of Washington, similar to data presented for the direct costs relating to the assessed interventions. Sorting Public Employees Benefit Board (PEBB) data using well known national migraine epidemiology should produce a very compelling picture of this impact.	Thank you for your comments. They appear to refer to the State's cost information provided and their process; these suggestions were not within the scope of work for Spectrum for this project

	Comment	Response
	Insight into the probable results of such an analysis is apparent from publicly available information on the 61,000 employees of the State of Washington's executive branch. Migraine is prevalent among women, veterans, and people aged 25 to 55 years, each of which account, respectively, for 52.5%, 9.2%, and 49% of the employee population. We understand the state is developing new employee-engagement workplace-culture measures for a modern work environment and employee safety and wellness. Given the likely greater-than-average prevalence of migraine among state employees, the Washington State Health Care Authority may consider recommending migraine management programs. Amgen would like to recommend a multifaceted migraine management program that was successfully implemented by American Express for its employees. Results from this program showed that employees were able to mitigate their migraine burden, although the program did not prevent migraines. **Citations listed:** 9 Office of Finance Management. Number of Employees and Headcount Trends. Accessed on March 22, 2017. Available at: ttp://hr.ofm.wa.gov/workforce-data-planning/workforce-data-trends/number-employees-andheadcount-trends 10 American Migraine Foundation. Understanding Migraine. Accessed on March 22, 2017. Available at: https://americanmigrainefoundation.org/ understanding-migraine/ampp/ 11 Nahini RL. Severe Pain in Veterans: The Effect of Age and Sex, and Comparisons with the General Population. J Pain.2017; 18:247-254. 12 Migraine Facts. Accessed on March 22, 2017. Available at: http://migraineresearchfoundation.org/aboutmigraine/migraine-facts/ 13 Office of Finance Management. Workforce diversity. Accessed on March 22, 2017. Available at: http://hr.ofm.wa.gov/workforce-data-planning/workforce-data-trends/workforce-profile-overview/workforcediversity 14 Office of Finance Management. Workforce Age. Accessed on March 22, 2017. Available at: http://hr.ofm.wa.gov/workforce-data-planning/workforce-	Citations provided did not meet our inclusion criteria. Comments related to State Programs are included for transparency but do not pertain to the Vendor's scope or report.

	Comment	Response
	data-trends/workforce-data-and-trendsoverview/workforce-age 15 Burton WN, et al. Evaluation of a Workplace-Based Migraine Education Program. J Occup Environ Med. 2016;58 (8):790-5.	
Outcomes	Additional outcomes pertaining to this disease need to be evaluated: • Identifying the right interventions for appropriate patients is an important consideration in assessing outcomes of migraine therapy • It's also important to note that there is an unmet need to be addressed. Specifically, up to 80 percent of people with migraine who start a preventive therapy discontinue within a year, due to intolerable side effects and lack of efficacy.	Thank you for your comments. The report is based on the policy context and interventions identified by the Technology Assessment Program. The outcomes chosen for this report were based on the key questions developed related to that context with clinical input. Information related to discontinuation of treatment due to side effects for the interventions selected for this report and the comparators is presented in the Safety section of the report.
Summary	In closing, we have noted that some HTAs inappropriately fall into a narrow silo or focus on the short term financial or budget impact of paying for interventions. Often, this involves estimating direct cost offsets – i.e. the net financial result of replacing one intervention with another. Yet, in order to create a sustainable health care system, it is important to look holistically at the burden and overall cost of disease—not just the cost of the interventions. Therefore, it is crucial that HTAs have a long-term view and be focused on the societal perspective, which is consistent with the recently updated recommendations for cost-effectiveness analyses from the Second Panel on Cost-Effectiveness in Health and Medicine.21 To its credit, HTA acknowledges the broad societal impact of headache disorders, including chronic migraine. However, a more thorough analysis of real-world evidence, cost of the disease, and additional health-related outcomes would provide a more complete assessment of the significant burden of migraine and the high unmet medical need.	Thank you for your comments Citations provided did not meet our inclusion criteria.

	Comment	Response
	Citations: 16 Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version), Cephalgia. 2013; 33: 629-808. 17 Amgen data on file, Marketscan data on file. 24-3-2017. 18 Lipton RB, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-349. 19 Hepp Z, et al. Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm. 2014;20(1):22-33. 20 Hepp Z et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88. 21 Sanders GD, et al. Recommendations for the Conduct, Methodological Practices, and Reporting of Costeffectiveness Analyses. Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016; 316:1093-1103.	

APPENDIX: Clinical/peer reviews and public comments received

CLINICAL/PEER REVIEW # 1: Janna Friedly, MD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Treatment of Chronic Migraine and Chronic Tension-Type Headache Report.** Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: http://www.hca.wa.gov/about-hca/health-technology-assessment/treatment-chronic-migraine-and-chronic-tension-type-headache

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: erika@specri.com

I will need your review by March 31, 2017 at the latest.

If you have questions or concerns please contact erika@specri.com. Thanks!

Reviewer Identification Information

Reviewer Name	**Janna Friedly**
Address	**Street 855 134th Ave NE**
	City Bellevue
	State WA
	Zip Code 98005
Phone	**206-280-5790**
E-mail	**friedlyj@uw.edu**

General comments: the table of contents numbering was a little bit confusing – the executive summary in the report included pages 1-1 through 1-56, but the TOC states 1-9. There are no line numbers so detailing the comments was a bit challenging.

The following comments relate to the executive summary and are listed by page number. In general, the executive summary findings are difficult to read and interpret. This is in part because many of the outcome measures and definitions have not yet been described or are buried in the text– so as a stand alone document, it is hard to interpret the findings. For

example, the definitions of short, intermediate and long term outcomes were provided on page 1-13, but the key findings do not use the terms short, intermediate and long term, so it requires remembering the definitions to be able to classify the findings. In general, I think it is easier for people to interpret the findings in terms of short, intermediate and long-term findings (as this is how we think clinically) rather than by number of weeks.

Page 1-11 Line

- Studies reporting populations with a mean of ≥12 headache days per month or ≥12 headache episodes or attacks per month were considered to meet the criteria for chronicheadache.

Why this definition? Is there a citation for this?

1-14 Line

- At 24 weeks, across 2 RCTs, there is moderate evidence that more BoNTA recipients achieved ≥ 50 % reduction in number of migraine days and overall number of headache days compared with placebo, however there was not a difference between groups in the percent of patients who achieved ≥ 50 % reduction in the number of migraine episodes across 3 RCTs (moderate evidence).
- Through 24 weeks, there were no statistical differences in the reduction of mean number of headache episodes (3 trials) or migraine episodes (2 trials) per month; however a small difference between groups for reduction (<2 days) in the mean number of headache days and migraine days per month favoring BoNTA was observed (moderate evidence for all outcomes).

These two bulleted findings are difficult to interpret. It is hard to understand the difference between the first and second – it takes quite a bit of reading to understand what these findings mean. I think these findings could be reworded to have parallel structure and highlight that there was a difference in terms of migraine and headache days (with either definition), but not in terms of migraine or headache episodes (with either definition).

- Summary of results: this comes before much of the info on outcomes so Headache Impact Test-6 Scores has not yet been defined. This makes it a little bit difficult to put these findings into context.

Page 1-16 Line

This statement is under the SMT vs amitriptyline category.

At 4 weeks, acupuncture resulted in a statistically greater proportion of patients achieving >20% and >40%, but not >60%, reduction in Headache Index scores from baseline compared with amitriptyline.

Chronic Tension-type Headache

BoNTA versus Placebo

- Short-term (8 weeks), although more patients the BoNTA experienced ≥ 25% reduction in painintensity, results did not reach statistical significance in 1 small RCT (insufficient evidence).
- At 12 weeks, although more patients the BoNTA experienced ≥ 45% reduction in pain intensity,results did not reach statistical significance in 1 small RCT (insufficient evidence)
- At 12 weeks, across 2 RCTs, BoNTA was associated with a reduction in the mean number of headache days per month (insufficient evidence).

It is unclear why the first 2 bullet points only refer to one study and the 3rd refers to 2 RCTs. This is a more general point, as this occurs in other sections – it is hard for the reader to understand with these summaries what the n is and why some findings only draw from a subset of the RCTs. There is a description in the report itself about how different studies used different outcomes and that is why there are different descriptions of % improvement and number of RCTs reporting certain outcomes, but this is not provided in the executive summary.

INTRODUCTION Comments

(This comment refers to the Appraisal section: pages 1-9)

Page 1	**Line**

A minor comment is that the paragraph that described OnabotulinumtoxinA (onaBoNT-A, Botox) on page 1 includes the statement “It has been associated with reduction in the number chronic migraine headaches attacks” which I think is best left out in the introduction as this is an assessment of the literature that will be reviewed in this study.

BACKGROUND Comments

In general, this is a well written background that addresses the need for this review and the importance of assessing commonly used treatments for migraine and chronic headaches. The definitions of the different types of headaches and the classification of chronicity was well described. There are clear descriptions of each of the different interventions considered in this review and the rationale for why these were included.

Page 37	**Line**

With the above in mind, the primary results for use of BoNTA for the prevention of chronic migraine from the 2013 AHRQ report are summarized in Table X.

Minor comment: Table X

REPORT OBJECTIVES & KEY QUESTIONS Comments

The key questions are clear and relevant.

METHODS Comments

The methods are clearly described and are appropriate to answer the key questions. One challenge is the diversity of outcome measures being assessed and the range of outcomes reported in the studies which makes comparisons difficult. This is not a flaw of the report or methodology necessarily, but reflects the challenges with the evidence and ability to compare studies. It is clear that there are few measures that have clear MCIDs and so the ability to interpret the outcomes and the magnitude of the treatment effects is problematic.

RESULTS Comments

The key questions are answered to the extent that they can be with the existing literature. In general, the summaries of the result are difficult to interpret because the statements are not referenced and the number of trials included (particularly for Botox vs placebo for migraines) in each summary statement (between 1-3) doesn't match the total number of trials included in the review (n=4).

In addition, when there are "positive" findings, it is difficult to interpret the magnitude of the effect or the clinical implications of these findings. I found that the summary tables that are included in the executive summary starting on page 1-26 present the conclusions in the most clearly understandable language and summarizes the magnitude of the findings and clinical significance. If the results section and the bulleted summary statements could use similar language, I think this report would be easier to interpret.

As I have pointed out below, there are many inconsistencies in the data presented and I found the tables and graphs a bit hard to interpret. I would recommend being as consistent as possible with formatting and adding footnotes when you have to stray from the common formatting in order to orient the reader.

Page 71 Line

It would be helpful to describe the magnitude of the treatment effect to put the MIDAS and HIT-6 results in perspective in terms of clinical importance.

Page 72 Line

This applies to this page but also to others that have the summaries of key findings – be consistent with use of periods at end of the summary statements. This is inconsistent throughout the document.

Another style suggestion for the bullets below – would suggest not bulleting the 1st as this is a heading for the 2nd two bullet points or more clearly designating this as a heading.

- BoNTA versus Amitriptyline (1 RCT):
- At 12 weeks, there were no differences between groups with regard to the percent of patients with ≥50% reduction in the frequency of pain days or the percent of patients with ≥3 point reduction in pain intensity; (low evidence for both outcomes)

- No data on short- or intermediate term outcomes were available

Page 72 Line

- At 12, 24, and 36 weeks, there was low evidence that more BoNTA recipients achieved ≥50% reduction overall number of headache days compared with placebo, however the differences did not reach statistical significance perhaps in part due to sample size.
- There were no differences at any time points up for the functional measures reported including MIDAS, HIT-6 and MIQ (low level evidence for all outcomes)

Presumbably, since there was just one RCT in this category, these two statements above refer to the same RCT. Was the lack of difference in functional measures due to small sample size as well or did the lack of differences and confidence intervals suggest this is a definitive finding?

Page 73 Line

Transcranial Magnetic Stimulation versus Sham

- At 4 weeks in one RCT, transcranial magnetic stimulation (TMS) resulted in a statistically greater improvement in all outcomes measured compared with sham (low quality evidence for all): proportion of patients achieving a >50% reduction in migraine attacks and in headache severity; reduction in the mean number of migraine attacks per month; and the proportion of patients improving to a functional disability rating of normal or mild.

- At 8 weeks in a second RCT, no statistical differences were seen between low-frequency TMS and sham for reduction in migraine attacks per 2 weeks and reduction in migraine days per 8 weeks; however, all data is of insufficient quality to draw conclusions.

This second bullet point is difficult to understand. "attacks per 2 weeks" and "days per 8 weeks" isn't clear. It is also difficult to reconcile the findings of the 1st RCT versus the findings of the 2nd RCT.

Page 73-75 Line

The descriptions of the studies in this section could be more clearly written to help the reader understand the difference between PREEMPT 1 and PREEMPT 2. Table 9 includes data from PREEMPT 1, PREEMPT 1 and 2 and PREEMPT 2. It isn't clear why you have chosen to include the combined data or what that adds. It is also unclear if the Aurora 2014 reference in this table is ALSO PREEMPT 1 and 2 as the n's are the same and the data very similar, but slightly different. It is also not clear why the Frietag 2007 study reports only combined data in one column rather than by assigned group as the other studies did. If this is because the data was not reported this way, a footnote should be included to explain this.

Also – is the Freitag 2007 study (n=60) different than the Freitag 2008 study (n=41)? I was unable to find the references for each of these studies.

Aurora 2014 – is this n=1384 a typo? In the following graphs, the n=1005. These types of errors make this report very difficult to follow.

It took reading this several times and then pulling the original papers to understand these studies and the data reported.

Page 76 Line

This statement below is unclear as written. I would suggest restating to say that although the proportion of patients who experienced >50% reduction was higher in each of these studies, these findings were not statistically significant or did not reach statistical significance…

The proportion of participants who experienced ≥50% reduction in number migraine episodes from baseline was higher following BoNTA compared to placebo, but groups were statistically similar across three trials.24,63,73

Page 76 Line

Results did not reach statistical significance in one small moderately low risk of bias trial at 16 weeks (RR 2.0, 95% CI 0.6, 6.8).73

In figure 5, the Freitag 2008 study which the above sentence references is classified as "moderately high risk of bias" versus the statement above which calls it "moderately low risk of bias"

Page 81 Line

Presenting figures 7 and 10 in opposite directions is a bit confusing. (i.e. one on the positive y axis and the other on the negative y axis). I would be consistent to make these graphs easier to interpret.

CONCLUSIONS Comments

I did not see any section in the report that corresponded to "conclusions." If this is referring to the summaries of the key findings, I have commented on these in the above sections. I do think it would be really helpful to have a conclusions section that summarizes the breadth of the available data, the overall quality of the data and the magnitude of findings in order to put this in context. This is a comment that pertains to all of these large reviews and is not specific to this particular review, but somehow it needs to be more clearly presented which of the findings are limited by high risk of bias studies. Although each of the studies is graded in terms of risk of bias and the strength of the evidence is graded in terms of insufficient, low, moderate, etc it takes quite a bit of reading and re-reading to really understand the big picture of this report. In general, there is insufficient or low quality evidence for all key findings with the exception of those related to the PREEMPT trials for botox. This somehow should be conveyed a bit more transparently.

QUALITY OF REPORT

Quality Of the Report
(Click in the gray box to make your selection)

Superior

Good (once the errors are corrected!)

Fair

Poor

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

This form is a bit cumbersome and the headings on this form didn't match the report exactly, so it was difficult to figure out where to put comments. There were no page numbers on my pdf report as well, which made it a bit more challenging to provide specific feedback.

CLINICAL/PEER REVIEW # 2: Robert Nicholson, PhD

Thank you for your willingness to read and comment on the Comprehensive Evidence-Based Health Technology Assessment Review for the **Treatment of Chronic Migraine and Chronic Tension-Type Headache Report.** Your contribution and time are greatly appreciated.

The general time commitment ranges between 2 and 4 hours; we are able to pay a maximum of 6 hours.

The report and appendices are available at: http://www.hca.wa.gov/about-hca/health-technology-assessment/treatment-chronic-migraine-and-chronic-tension-type-headache

This form can be filled out electronically on your personal computer. Enter your identification information and comments directly into the shaded areas; use the **TAB** key to move from field to field. Please enter the section, page, and line numbers where relevant. The shaded comment field will expand as you type, allowing for unlimited text. You have been provided comment fields in each section. Should you have more comments than this allows for, please continue with a blank page. Additionally, we are very interested in your evaluation of the ease of use of our Peer Review Form. Please use the last field to enter suggestions for improvement.

We will be going through the draft for typographical errors as well as grammatical and minor edits, allowing you to focus on the substance/content of the report.

When the Peer Review form is complete, save it to your hard drive and return as an e-mail attachment to: erika@specri.com

I will need your review by March 31, 2017 at the latest.

If you have questions or concerns please contact erika@specri.com. Thanks!

Reviewer Identification Information

Reviewer Name	**Robert A. Nicholson, PhD**
Address	14528 S. Outer Forty, Suite 100 Chesterfield, MO 63005
Phone	314-628-3421
Fax	314-628-3400
E-mail	Robert.Nicholson2@mercy.net

INTRODUCTION Comments

Page 1

- "Tension-type headache….accounts for 90% of all headaches." Would recommend a citation for this reference. Also, given that this report is on treating patients who present for headache care, it may be useful to note that although Tension-Type Headache (TTH) is more common than migraine, most individuals who present for care do so for migraine.

Most TTH headaches are adequately controlled with OTCs and rarely present for care. Moreover, given that the report is focused on chronic headache, this statement may deter the audience's focus on the population being considered.

Psychological Treatment

- "Migraine management generally focuses on pharmacological therapy". There are a host of articles, reviews, and expert opinions regarding the value of psychological therapy for migraine. A summary can be found here http://www.headachejournal.org/view/0/EvidenceBasedBehavior.html.
- The sentence a line above states "Usual management of TTH includes pharmacotherapy, psychological therapy…". This could easily be changed to ""Usual management of TTH and migraine includes pharmacotherapy, psychological therapy…" and be accurate.

Page 2

Policy Context

- Interventions being assessed. Reading through the evidence report, it became clear what was being studied. However, the context for inclusion was not fully clear. It seems that the focus could be stated as "interventions in which the heath care professional is physically intervening in some manner". The focus is not non-pharmacological interventions as Botox and trigger point injections both include pharmacologic agents. Moreover, this does not included psychological interventions and so there really is a specific realm in which this evidence reports is focused. However, it is difficult to find a strong logic case for the value in choosing this particular set of interventions.
- Similarly, although it becomes clear as one reads the report that the primary focus is on reducing headache episodes/frequency, it would be helpful to state this in the background/rationale section prior to the objectives.

Page 5

Outcomes Assessed….

- Point 2 states "Complete cessation//prevention of headache: This operationally included reduction in mean number…." This seems incongruent. If there is complete reduction then the reduction in mean number would be 100%. Reading through the report it does not appear that complete cessation/prevention is measured.
- Of note, any intervention that has aimed for complete cessation/prevention has always failed. There are a host of potential reasons as to why this is a nearly impossible aim and not one worth evaluating relative to other outcomes.

Table 1.

- Outcomes measures. Ultimately, the primary outcome for these studies was reduction in headache episode or day frequency. The outcome measures noted in Table 1 were measures in addition to the primary outcome, which seemed odd upon first review.
- Outcome measure domains. This reviewer was surprised to see functional, disability, quality of life, pain-related, and psychologically related outcomes all being combined into one table. Each

of these is inherently measuring something different and one could easily expect the outcomes to vary and not be related specifically to whether the intervention was effective at reducing headache. Perhaps separating those or at least acknowledging that they are measuring different constructs and the limitations inherent in considering them together would be useful.

BACKGROUND Comments

General Comments:

- The overall background is well written and clear. The discussion regarding the evolving nomenclature and vernacular surrounding the classifications and labels of various chronic headache types is valuable to set the context for the review.

Page 18

- Near the bottom of the page it is stated "Several newer interventions have recently surfaced." Among those listed are acupuncture, massage, manipulation, trigger point injections. Although one might argue that the systematic evaluation of these for preventing chronic headache is relatively new, these interventions have been used clinically for a long period of time.

Page 21 & 23

Medication Overuse

- Medication overuse can influence progression from episodic to chronic headaches. This is seen consistently in clinical practice and its relevance has emerged over the past decade. In the review, this is noted as being potentially relevant for barbiturates and opioids. However, it would be useful for the review to note that few trials appeared to specifically ask about potential medication overuse and as such, a potential treatment confounder was not typically accounted. At the same time, this lack of accounting for medication overuse headache must take into context the evolving nature of the field's understanding of this phenomena a decade ago.
- Although the authors note that NSAIDs and triptans do not appear to be related to medication overuse headache, here is a citation that suggests the evidence may be mixed https://www.ncbi.nlm.nih.gov/pubmed/23992516
- The authors may want to specifically note that although the role of medication overuse in contributing to chronic headache progression and maintenance is of varying importance, it is something that would be ideally accounted for when selecting patients for trials such as those under consideration for the current review. The authors may want to note that unscreened and/or untracked medication overuse could have a non-zero impact on trial results. However, the authors would do well to acknowledge that for some of these studies, particular those initiated and conducted in the early 2000's, the potential influence of medication overuse was not appreciated to the degree it is now.

Page 23

Psychological Treatment for Chronic Headache

- Please see the comments noted in the background/rationale section earlier about how these treatments (including biofeedback) are potentially useful for CM and CTTH.

Headache Type Classification

- The review notes that those presenting with both migraine and tension-type headache are considered chronic daily headache and is not an ICHD 3 classification. This is accurate. However, one wonders about whether this is a function of some older studies that were conducted prior to the newest ICHD classification and/or prior to a consistent nomenclature being discussed in the literature (which emerged over the 2000's). This is relevant in that those who are classified as CM or CTTH often experience both types of headaches (or at least headaches that don't always fit every time into the diagnosed category). It is the predominant type that ends up getting diagnosed and thus classified.
- Given the journey to achieve a consensus nomenclature and subsequent ICHD 3 classification was occurring in parallel with the time frame for many of these studies, it might be useful to more clearly state the dates for which the various names and classifications emerged relative to the studies evaluated. Perhaps a study from the early 2000's may have been considering a "CDH" group that now might be "CM".

Page 33

- AAN…The "N" here refers to Neurology rather than Neurosurgeons https://www.aan.com/Guidelines/Home/ByTopic?topicId=16

THE EVIDENCE Comments

General Comment:

- Aims/objectives all seem to address relevant policy and clinical issues.
- Please see previous comments related to content on page 5 regarding outcomes assessed.
- See same section comments for page 5 regarding outcome domains assessed. The table on p. 63 does a better job of delineating the domains.

Page 66

- It was unclear how total citations with n = 47 led to exclusions of n = 2795. One suspects that n = 47 was in actuality n = 2947, of which 2795 were excluded, but this would benefit from being made more clear.

Page 66

- Appendix E. Although it is expected that the rationale for not including Appendix E was space, the tables in Appendix would have been highly useful to include in the report and/or use the structure of that table to improve the utility of tables included in the results section.

METHODS Comments

General Comments

- Method for identifying relevant studies is adequate?
    - Yes
- Criteria for the inclusion and exclusion of studies is appropriate?
    - Yes
- Method for Level of Evidence (LoE) rating is appropriate and clearly explained?
    - For the most part. Including the information in Appendix E within the report would help improve clarity.
- Data abstraction and analysis/review are adequate?
    - Yes

RESULTS Comments

General Comments

- Amount of detail presented in the results section appropriate?
    - For the most part. The sections aren't as uniformed in their look and feel as one might expect. Not every section feels like it was handled in the same manner. In situations like this where there are lots of repetitive sections, one would expect there to be easily observed consistency in the format.
- Key questions are answered?
    - Yes, very well.
- Figures, tables and appendices clear and easy to read?
    - No. Tables 9, 11, and others like it are confusing for the reader. The tables in the appendix are much easier to follow.
    - Would recommend putting the reference number next to the study author names in the tables.
- Have gaps in the literature been dealt with adequately?
    - The authors appear to have dealt with the known literature and noted where there are deficiencies in the literature.
- Recommendations address limitations of literature?
    - Not applicable at this time.
- Explanation of RoB. For some of the trials the RoB was explained (eg, p. 90 and others); however, there were examples where this was not the case (eg, p 86). Would recommend they all be explained and consistently presented.

Page 102

This is the one place where this reviewer found a note that the presence of medication overuse had an unknown impact on outcomes.

Page 169

Under results: Base Case, $ was used instead of £.

Page 215

This section seemed oddly placed, inserted after the evidence tables.

CONCLUSIONS Comments

Are the conclusions reached valid?

- Not applicable at this time

OVERALL PRESENTATION and RELEVANCY Comments

- Is the review well structured and organized?
  - For the most part, yes. See comments regarding Tables 9, 11, and others like it regarding confusion.
- Are the main points clearly presented?
  - Yes
- Is it relevant to clinical medicine?
  - Yes
- Is it important for public policy or public health?
  - Yes

QUALITY OF REPORT

Quality Of the Report

Superior

Good X

Fair

Poor

- Superior content with room for improvement in presentation clarity and consistency.

USABILITY Comments

We would appreciate any feedback you have on the usability of this form. Please add comments in the field below.

- In each comment section, it asks for page and line numbers...there were no line numbers in the report
- There is no “Introduction” but rather “Appraisal”…similar issues elsewhere such that the headings in the report did not match the review headers.
- The functions underlying the greyed in boxes did not work, at least for my computer (using MS Word 2013 on a PC running Windows Enterprise 7)

Medical Information

AMGEN

Amgen
One Amgen Center Drive
Thousand Oaks, CA 91320-1799
Direct Dial: 800-772-6436
Fax : 866-292-6436
www.AmgenMedInfo.com

April 5, 2017

Health Technology Clinical Committee (HTCC)
Washington State Health Care Authority
P.O. Box 42712
Olympia, Washington 98504-2712
shtap@hca.wa.gov

RE: Health Technology Review: Treatment of Chronic Migraine and Chronic Tension-Type Headache Draft Report

Dear Sir or Madam:

Thank you for the opportunity to provide comments on the Health Technology Review on the Treatment of Chronic Migraine and Chronic Tension-Type Headache Draft Report as part of the public comment period. On behalf of Amgen, Inc. (Amgen), please find enclosed the information on the draft report, as requested.

Amgen is providing you with referenced information. If you would like a reprint of a reference, contact Amgen Medical Information. Please note that if you are a covered recipient as defined by the Affordable Care Act (ACA), and Amgen provides you with the requested reprint(s), Amgen's cost to obtain such reprint(s) may need to be disclosed and reported in accordance with the requirements under the ACA, state law and related disclosure obligations by Amgen. If you are a non-covered recipient requesting information on behalf of or the benefit of a covered recipient (physician or teaching hospital), the same requirements may apply.

This information has been provided to you in response to your unsolicited request. If we may provide further information or assistance, or if you did not request this information, please contact Amgen Medical Information at 800-77-AMGEN (26436), MedInfo@Amgen.com or visit our website at www.amgenmedinfo.com.

Sincerely,

Suzana Giffin, PharmD
Executive Director, Global Scientific Communications

MIR-437976

Amgen appreciates the opportunity to comment on the Washington State Health Technology Assessment (HTA) program's Draft Evidence Report on the treatment of chronic migraines and chronic tension-type headache.

Migraine is a serious disease with real costs to patients, families, employers and the healthcare system. Better preventive options are needed for the 3.5 million people who are currently seeking prevention for their frequent migraine**.** [1,2] Approximately 80 percent of these people who start a preventive therapy discontinue within a year, due to intolerable side effects and lack of efficacy. [3,4] As one of the world's leading biotechnology companies, Amgen develops medicines that meet important unmet medical needs, including preventive options for people with both chronic and episodic migraine.

We have therefore reviewed with great interest the draft evidence report, "Treatment of chronic migraine and chronic tension-type headache," published for comment by the HTA Program of the Washington State Health Care Authority on March 6, 2017.

We recognize that the HTA remit encompasses medical devices, procedures and tests, not pharmacological products, and that the draft report accordingly focuses on the treatment of chronic migraine and chronic tension-type headache with OnabotulinumtoxinA, trigger point injections, transcranial magnetic stimulation, manual therapies and acupuncture. Despite not having a pharmacological intervention included in the assessment, we would like to comment on the draft report for the following reasons:

- The treatment of migraine is multimodal and multidisciplinary. Clinicians consider a range of treatment options and frequently switch patients between alternative treatment options.
- Amgen is committed to having an ongoing dialogue with patients, providers, payers, policymakers and regulators to find ways to stimulate innovation of all types, while also alleviating the financial and societal burden of some of the world's most serious diseases. We therefore seek to engage constructively on the overall approach of HTA initiatives.
- The draft report explains, "Migraine management generally focuses on pharmacological therapy. In chronic headache disorders, including chronic tension-type headache (CTTH) and chronic migraine (CM), the focus of treatment is on preventative measures." Amgen recognizes that this is an area of high unmet need for people with migraine.

Specifically, we provide comments on the overall approach to HTAs, the cost of disease for headache disorders including migraine, and additional outcomes that should be evaluated.

Overall Approach

Given the stakes for patients, Amgen believes that all economic reviews on the value of medicines should aim to achieve the highest level of transparency, strive for very broad stakeholder engagement,

[1] Amgen data on file, Marketscan data on file. 24-3-2017.
[2] Lipton RB, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-349.
[3] Hepp Z, et al. Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm. 2014;20(1):22-33.
[4] Hepp Z, et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88.

and place scientific rigor and patient interests at the center of the analyses. We believe that a thorough and balanced technology assessment should rely on direct data from rigorous comparative trials when available, calibrated and adjusted for real world application in the heterogeneous markets and treatment settings where the technologies are expected to be used.

Amgen therefore applauds the HTA program for its systematic review of the literature based on transparent inclusion/exclusion criteria and its reporting, with rigorous evaluation of *each included study's results*. For example, the review of chronic migraine cost-effectiveness studies provides the weaknesses of each study evaluated in the HTA and notes when the source is from a study with pooled data. However, the draft report failed to note certain instances where validated study data were not included (see the bulleted list under *Cost of Disease* section for details). A more thorough HTA needs to evaluate all strengths and weaknesses of the economic studies included in the assessment. Finally, it is imperative for a robust HTA to integrate real-world observational evidence in addition to results from randomized control trials in order to capture and model the broad impact of a disease on patients and society in the setting of actual practice.

Cost of Disease

Often HTAs only view the cost of disease from a narrow silo or focus on the short-term financial or budget impact of paying for interventions by estimating direct-cost offsets – i.e. the net financial result of replacing one intervention with another. It is imperative for the scientific rigor of any HTA to evaluate the overall burden and cost of disease holistically and not just the cost of the interventions to create a sustainable health care system. In addition, it is essential to consider the inefficiencies associated with migraine-care delivery and how some of these inefficiencies may be rectified by the use of a more innovative therapy.

To its credit, this HTA does acknowledge the broad societal impact of headache disorders, by noting:

> "Headache disorders are associated with substantial impact on the physical, psychological, and social well-being of patients, in addition to having substantial healthcare costs. They are a leading cause of disability and diminished quality of life, making them one of the most common reasons for patient visits in primary care and neurology settings and emergency department visits." (p. 1)

The HTA also cites several studies estimating indirect costs of migraines, primarily due to reduced work productivity (presenteeism) and missed workdays (absenteeism). However, the systematic review has identified only clinical and cost-effectiveness studies and fails to include recent studies that have further validated the significant indirect costs associated with episodic migraine and CM:

- Migraine patients incur significantly higher indirect costs (absenteeism, short-term disability, and long-term disability costs) than matched non-migraine patients ($11,294 vs $8,945)[5]
- Migraine patients are more likely to have short- and long-term disability claims, and incur ~$1,300 higher per patient disability-related costs than non-migraine patients.[6]

[5] Bonafede, MM et al. Incremental Direct and Indirect Costs Associated With Migraine in the United States. Presented at: ISPOR 19th Annual European Congress, October 2016, Vienna, Austria.
[6] Ibid.

- The indirect economic burden (absenteeism and presenteeism) of migraine is estimated to be ~$13Bn in the US, costing employers up to $4K and $13K per year for episodic and chronic migraine sufferers, respectively.[7]

In addition, a 2017 systematic review of 28 studies found that presenteeism costs are rarely included in full economic evaluations, although the impact of presenteeism in the workplace and society is high. With respect to migraine, Kigozi et al observed:

> "Presenteeism, from this review, appears to contribute significantly to productivity costs (or savings) and overall total costs of certain disease areas such as musculoskeletal pain, migraine, and mental health–related disorders. Economic evaluation recommendations in these disease conditions that do not include estimates of presenteeism may result in less than optimal resource allocation decisions from a societal perspective."[8]

In light of this important information, the HTA could demonstrate the public employee impact of migraine on indirect costs in the State of Washington, similar to data presented for the direct costs relating to the assessed interventions. Sorting Public Employees Benefit Board (PEBB) data using well-known national migraine epidemiology should produce a very compelling picture of this impact.

Insight into the probable results of such an analysis is apparent from publicly available information on the 61,000 employees of the State of Washington's executive branch. Migraine is prevalent among women, veterans, and people aged 25 to 55 years, each of which account, respectively, for 52.5%, 9.2%, and 49% of the employee population. [9,10,11,12,13,14]

We understand the state is developing new employee-engagement workplace-culture measures for a modern work environment and employee safety and wellness. Given the likely greater-than-average prevalence of migraine among state employees, the Washington State Health Care Authority may consider recommending migraine management programs. Amgen would like to recommend a multifaceted migraine management program that was successfully implemented by American Express

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[7] Serrano D, et al. Cost and predictors of lost productive time in chronic migraine and episodic migraine: results from the American Migraine Prevalence and Prevention (AMPP) Study. Value Health. 2013;16(1):31-8.

[8] Kigozi J, et al. The Estimation and Inclusion of Presenteeism Costs in Applied Economic Evaluation: A Systematic Review. Value Health. 2017;20(3):496-506.

[9] Office of Finance Management. Number of Employees and Headcount Trends. Accessed on March 22, 2017. Available at: http://hr.ofm.wa.gov/workforce-data-planning/workforce-data-trends/number-employees-and-headcount-trends

[10] American Migraine Foundation. Understanding Migraine. Accessed on March 22, 2017. Available at: https://americanmigrainefoundation.org/understanding-migraine/ampp/

[11] Nahini RL. Severe Pain in Veterans: The Effect of Age and Sex, and Comparisons with the General Population. J Pain.2017; 18:247-254.

[12] Migraine Facts. Accessed on March 22, 2017. Available at: http://migraineresearchfoundation.org/about-migraine/migraine-facts/

[13] Office of Finance Management. Workforce diversity. Accessed on March 22, 2017. Available at: http://hr.ofm.wa.gov/workforce-data-planning/workforce-data-trends/workforce-profile-overview/workforce-diversity

[14] Office of Finance Management. Workforce Age. Accessed on March 22, 2017. Available at: http://hr.ofm.wa.gov/workforce-data-planning/workforce-data-trends/workforce-data-and-trends-overview/workforce-age

for its employees. Results from this program showed that employees were able to mitigate their migraine burden, although the program did not prevent migraines.[15]

Outcomes

Finally, additional outcomes pertaining to this disease need to be evaluated. Identifying the right interventions for appropriate patients is an important consideration in assessing outcomes of migraine therapy. For example, not all adults affected by migraine are eligible for preventive medication according to medical guidelines.[16] Of these patients, approximately 3.5 million currently take preventive treatment.[17] [18] It's also important to note that there is an unmet need to be addressed. Specifically, up to 80 percent of people with migraine who start a preventive therapy discontinue within a year, due to intolerable side effects and lack of efficacy.[19,20]

Summary

In closing, we have noted that some HTAs inappropriately fall into a narrow silo or focus on the short-term financial or budget impact of paying for interventions. Often, this involves estimating direct cost offsets – i.e. the net financial result of replacing one intervention with another. Yet, in order to create a sustainable health care system, it is important to look holistically at the burden and overall cost of disease—not just the cost of the interventions. Therefore, it is crucial that HTAs have a long-term view and be focused on the societal perspective, which is consistent with the recently updated recommendations for cost-effectiveness analyses from the Second Panel on Cost-Effectiveness in Health and Medicine.[21] To its credit, HTA acknowledges the broad societal impact of headache disorders, including chronic migraine. However, a more thorough analysis of real-world evidence, cost of the disease, and additional health-related outcomes would provide a more complete assessment of the significant burden of migraine and the high unmet medical need.

Thank you for the opportunity to comment.

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[15] Burton WN, et al. Evaluation of a Workplace-Based Migraine Education Program. J Occup Environ Med. 2016;58 (8):790-5.

[16] Headache Classification Committee of the International Headache Society (IHS). The International Classification of Headache Disorders, 3rd edition (beta version), Cephalgia. 2013; 33: 629-808.

[17] Amgen data on file, Marketscan data on file. 24-3-2017.

[18] Lipton RB, et al. Migraine prevalence, disease burden, and the need for preventive therapy. Neurology. 2007;68(5):343-349.

[19] Hepp Z, et al. Systematic review of migraine prophylaxis adherence and persistence. J Manag Care Pharm. 2014;20(1):22-33.

[20] Hepp Z et al. Adherence to oral migraine-preventive medications among patients with chronic migraine. Cephalalgia. 2015;35(6):478-88.

[21] Sanders GD, et al. Recommendations for the Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses. Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016; 316:1093-1103.